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Care Transitions and Adult Day Services Moderate the Longitudinal Links between Stress Biomarkers and Family Caregivers' Functional Health

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Abstract

Background—Stress biomarkers have been linked to health and well-being. There are, however, few studies on how dysregulation in hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) actually affects functional health among family caregivers of relatives with dementia. Further, it is not clear whether and how factors affecting caregiving stressor exposures such as care transitions and Adult Day Services (ADS) use may affect such association.

Objective—First, to examine the association of daily stress biomarkers and functional health over time among dementia family caregivers. Second, to examine effects of care transitions and ADS use on the association between baseline stress biomarkers and functional health over time.

Methods—At baseline, caregivers provided five saliva samples each day during an 8-day diary study, where all caregivers were having a varying number of ADS days per week. There were two longitudinal follow-ups at 6 and 12 months on ADS use, care transitions, and caregivers' functional health. The average daily total output across days were computed at baseline for salivary cortisol, the sulfated form of dehydroepiandrosterone (DHEA-s), and salivary alpha amylase (sAA), which were used as predictors of caregivers' longitudinal functional limitation trajectories. Care transitions and total number of ADS days per week at baseline were considered as moderators of the associations between stress biomarkers and health over time.

Results—The associations between functional limitation trajectories and daily total outputs of cortisol and sAA were modified by ADS use and caregiving transitions. Among caregivers who experienced a transition, and who used less than average ADS days per week, lower daily cortisol total output and lower daily sAA total output were associated with increasing functional limitations. Caregivers who experienced a transition but used greater than average ADS days per week did not show such patterns of association. No significant effect was found for DHEA-s.

Conclusion—The study contributes to an important but largely unanswered question on implications of stress biomarkers on functional health. Assessments on the association between

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stress biomarkers and health among dementia family caregivers need to consider changes in stressor exposures over time, such as care transitions and ADS use.

Keywords

Stress biomarkers; Functional health over time; Family caregiver; Adult Day Services; Care Transitions

Biobehavioral theories and empirical studies have established links between stress, biomarkers of stress, and physical health [1,2]. Particularly, biological responses to chronic stress manifested by dysregulation in hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) has been found to be related to poor health outcomes [1]. For family caregivers of relatives with dementia, high levels of chronic stress are associated with psychological as well as health changes [3]. Biological markers of the stress response may be the underlying mechanism between chronic stressor exposure and health decline.

Stress reactivity as a multidimensional construct

The major part of the neuroendocrine systems that is closely associated with stress functioning is the HPA axis, which regulates many important bodily processes in response to stress such as metabolism and immune functions. Two of the primary hormones/mediators of the HPA axis are cortisol, and dehydroepiandrosterone (DHEA) and its sulfated form DHEA-s. Chronic stressors can disrupt cortisol output. Particularly, cortisol deficiency (*hypo-cortisolism*) has been related to disease pathogenesis such as posttraumatic stress disorder, rheumatoid arthritis, and chronic fatigue [4]. DHEA-s is coreleased with cortisol in response to stressor exposure. However, DHEA-s is anabolic, while cortisol is a catabolic hormone [5]. Anabolic hormones such as DHEA-s (i.e., androgens) are important for stress and aging. At sufficient levels, anabolic hormones have restorative functions, whereas deficits in anabolic hormones may leave cortisol actions unopposed, and are associated with premature aging and increased risks of early mortality [5]. Studies have consistently reported that chronic stress and its association with low levels of both DHEA-s and cortisol [6].

Extensive research also suggests that stressors activate the sympathetic nervous system (SNS). One SNS marker, salivary alpha-amylase (sAA), can serve as a sensitive, reliable, and non-invasive measure of experienced stress [7,8]. As an enzyme, sAA is produced in the oral cavity by major salivary glands. Its release is elicited by the SNS activation, which controls the salivary glands. Levels of sAA parallel the response of norepinephrine to stressors. As with the HPA markers, sAA is often low in chronic stress situations [9].

Biomarkers as indicators of pre-disease pathways

The concept of pre-disease pathways describes the biological influences that occur prior to the onset of diseases, functional decline and mortality [10]. An important tenet of research on health is to evaluate these precursors to morbidity onset at distant time points, and to employ multiple indicators simultaneously, rather than focusing on a single biological marker [11]. Furthermore, multiple observations of a given biomarker over time can be a

more informative and reliable measurement of biological responses to stressors [12]. Linking daily biomarkers to long-term measures of health allows for examination of possible pre-disease pathways and helps quantify the implications of stressor exposures for health.

Cortisol, DHEA-s, and sAA may have distinct associations with health and stress. Dysregulated cortisol in reactivity to chronic stress has been related to diseases such as rheumatoid arthritis and asthma [4]. Greater sAA stress reactivity was observed in children who had more parent-reported health problems and illnesses [13]. Further, lower DHEA-s levels were shown to be associated with increasing functional limitation, poorer subjective health, and increasing depressive symptoms [14]. HPA and SNS reactivity in response to chronic stress of caregiving, although rarely examined, may have similar health implications among dementia family caregivers. For example, hypocortisolism and lower sAA levels may be associated with poor functional health among dementia caregivers.

Health and functional limitations

Health is a multidimensional construct. One useful measure is functional limitations, which is a common outcome of multiple health conditions. Functional limitations are sensitive to the health effects of chronic stress, particularly for a sample in middle and late life, for whom stressors may exacerbate pre-existing conditions as well as lead to incident illness [3,15]. Furthermore, measures of functional limitations are less likely to be affected by the biases inherent in another widely used global measure, subjective health, where ratings often reflect comparisons with peers, rather than overall functioning [16]. Therefore, the objective measure of functional limitations is of particular salience in later life.

The impact of Adult Day Services and care transitions on stressor exposures and health

Dementia caregivers experience on average high levels of daily stress during day and night, which can be associated with their compromised health and well-being [17]. Two factors that directly affect exposures to daily stressors are use of respite and transitions in the caregiving role, which in turn relate to caregiver health. Caregiving respite such as Adult Day Services (ADS) programs provide a predictable amount of time away from the care receivers during the day. Research shows ADS can reduce daily exposure to care-related stressors by 40 percent and creating opportunities for caregivers to engage in self-care activities [17]. Regular ADS use has been found to be effective in lowering depressive symptoms and anger [18,19]; other studies have also found that caregivers report better self-efficacy in behavior management and enhanced general well-being as a result of ADS use [20]. Additionally, ADS use may be associated with better regulation of daily biomarkers. Caregivers showed improved cortisol awakening response (CAR) and daily total cortisol output among those with flattened CAR and low daily output on non-ADS days [21,22]; on days following ADS use, DHEA-s levels were also higher [23]. Research also shows that caregivers who received more days of respite were less likely to experience functional declines compared to caregivers using fewer days of adult day care [3]. Therefore, we expected ADS use would moderate the association between stress biomarkers and functional health.

Another factor affecting caregiving stress is care transitions. Although the transition itself is stressful in the short-run, it has the effect of decreasing exposures to care-related stressors and other caregiving responsibilities over time. One major transition across the course of caregiving is institutionalization or turning care over to another family member. Similar to but different from ADS use, which reduces care-related behavioral and emotional problems during daytime only, institutionalization can additionally reduce caregivers' exposure to care-related sleep disturbances at nighttime. Research shows nocturnal disturbances and disruptions in sleep routines present a significant source of objective stressor among dementia caregivers, which closely relates to higher subjective burden, more depressive symptoms, and impairment in daytime function [24,25]. Similar to daytime ADS use, institutionalization and modifications of care-related stressor exposures may arguably relate to better regulations of stress biomarkers. Therefore, compared with ADS use alone, institutionalization and getting further relief from the demands of around-the-clock care may have an ameliorating effect on caregiver health and functioning over time [26].

Studies have found that institutionalization is associated with declining health of the caregiver [3]. And more precisely, declining health may be a precipitant for caregivers' decision to place their relatives [26]. Buhr, Kuchibhatla, & Clipp [27] studied the reasons for nursing home placement based on a 3-year longitudinal study. Among caregivers who institutionalized their relatives, nearly half of them indicated their own health problems as the primary reason. Thus, it is important to consider effects of institutionalization when studying the possible associations between biomarkers at baseline and long-term health. Additionally, although admission into a nursing home or similar institutional setting is the most common type of placement, caregivers may turn care over to another family member. As with institutionalization, this transition may have positive benefits for caregivers by lowering daily care-related stressor exposures, but may also reflect a downward trajectory in caregivers' health. Thus, it should also be considered when evaluating long-term health outcomes. Therefore, the current study define care transitions as institutionalization or turning care over to another family member, so that caregivers were no longer providing active care to their relatives at 6 or 12 months when the relative still needed the care.

The current study

The current study builds on prior research [3] and evaluates the extent of association between stress biomarkers and changes in functional health over a one-year period among dementia family caregivers. Caregivers who initially participated in a study of the effects of ADS use on three biomarkers, cortisol, DHEA-s and sAA, were followed for a one-year period to examine associations of biomarkers obtained at baseline on their subsequent functional health. This study is among the first that explores the health implications of stress biomarkers over time using multiple indicators of both HPA and SNS systems. Two factors that might moderate the effects of biomarkers on functional health outcomes were taken into account (see Figure 1). First, although all caregivers in the study were initially using ADS services, they varied in how much respite they received, and thus how much reduction they experienced in stressor exposures [19]. Therefore, amount of ADS use was considered for its effect on functional health changes over time. Second, as care transitions may be associated with functional health over time, whether caregivers placed their relative in a nursing home

or turned care over to someone else was also considered as a covariate. The hypotheses for this study are the following:

- Hypothesis 1** We expect that the three stress-related biomarkers, cortisol, DHEA-s, and sAA, will be associated with declines in functional health. Additionally, this relationship will be moderated by caregiver transitions. Specifically, functional health declines will be associated with lower daily total outputs of cortisol, DHEA-s, and sAA, but the associations between functional health and stress biomarkers will be most pronounced among caregivers who had a transition out of the role, compared to others who continued providing care.
- Hypothesis 2** We expect that ADS use at baseline will further moderate the association between the three biomarkers and health. Specifically, among caregivers who had a transition, and who used fewer ADS days at baseline, lower daily total output of all biomarkers will be associated with declining health over time.

Methods

Participants and procedures

Participants were 184 primary caregivers who were providing care to a relative with dementia at baseline. Caregivers participated in an 8-day diary study and provided five saliva samples each day as part of the *Daily Stress and Health* (DaSH) study [19]. Eligibility included that a) caregiver and their relative lived in the same household, b) the relative had a physician's diagnosis of a type of dementia (e.g. Alzheimer's disease), c) the relative attended ADS programs at least two days a week, and d) the relative was alive throughout the entire study period. Caregivers subsequently completed follow-up telephone interviews at 6 months (*missingness* = 2) and 12 months (*missingness* = 10). One hundred and seventy two caregivers participated at least two data collections at baseline, 6 and 12 months. The final working sample of caregivers ($N = 141$) did not include those whose relatives were deceased at either 6 months or 12 months ($n = 31$). There was a compelling reason for not combining bereaved caregivers with those who turned care over, because of differences in the implications of the transitions for health. Additionally, the number of bereaved caregivers was too small to examine them separately. Table 1 presents detailed transition types and the corresponding number of caregivers at specific follow-up time. Table 2 presents demographic characteristics of caregivers and their relatives.

Recruitment was conducted at ADS programs in Northern and Central New Jersey, the Philadelphia and Pittsburgh metropolitan areas, Northern Virginia, and Denver, Colorado. Caregivers from 57 programs contacted us over a 3-year period. Eligible caregivers completed an initial in-person interview. The interviewer obtained signed consent and sociodemographic information. The interviewer also trained participants in the use of a home saliva kit. The kit contained 40 color-coded salivettes (Starsdet, Cary, NC) and a home collection diary. For the next 8 days, participants collected saliva 5 times a day (i.e., before getting out of bed, 30-min after getting out of bed, before lunch, before dinner, and before

bed). Saliva collection times were recorded on salivettes and the home collection diary. Participants kept salivettes in the refrigerator until the shipment to the lab at the end of daily sampling period. Daily telephone interviews were conducted in the evenings of the 8 days by interviewers from the Penn State Survey Research Center. In the interviews, participants reported daily stressors and affect, confirmed times of the saliva samples and reported use of ADS services. On the last day they received salivette shipping instructions. Participants were paid \$150 for completing the entire study protocol.

Once received at the Penn State Biomarker Core Lab, saliva samples were weighed, racked, and stored at -80 degree C. Salivary cortisol, DHEA-s, and sAA were determined using commercially available enzyme immunoassay kits (DiaMetra, Italy). At time of assay, samples were brought to room temperature and centrifuged to separate mucin from clear saliva. Samples from each participant were tested in duplicate in a single assay batch. Duplicate test values that varied by more than 5% for cortisol and sAA, and 10% for DHEA-s were subject to repeat testing. Values used in data analyses are the averages of duplicate tests. A saliva sample was invalid [21,28] if: 1) the caregiver was awake for less than 12hr or greater than 20hr ($n = 14$), or 2) the caregiver woke up after 12pm ($n = 0$), or 3) for cortisol assay specifically, there was a greater than 10 nmol/L rise between the second (30 minutes after getting out of bed) and third sample (before lunch) ($n = 11$), or 4) the recorded collection time between the first (upon wakeup) and second sample (30 minutes after getting out of bed) is either less than 15min or greater than 60 minutes ($n = 99$).

Measures

Functional health limitation—Functional health limitation was measured with a 9-item scale ($\alpha = .82$) from the Medical Outcomes Studies (MOS) 36-item short form health survey (SF-36) [29]. It assessed degrees of limitation in physical activities: moderate activities such as pushing a vacuum, moving a table; carrying groceries; climbing stairs; bending, kneeling or stooping; walking; bathing and dressing [30]. Caregivers were asked about how much physical limitation (3-point scale; coded 1 = *not limited*, 2 = *limited a little*, 3 = *limited a lot*) they had in carrying out these activities, and higher scores indicated greater functional limitations.

Daily biomarkers—The sample test volume for salivary cortisol was 25 μ l. The assay had a lower limit of sensitivity of 0.03 μ g/dl, with an average inter-and intra-assay covariance of less than 7% and 4%, respectively. Cortisol measurement units were converted to nmol/L (μ g/dl $\times$ 27.6). The sample test volume for salivary DHEA-s was 50 μ l. The assay had a lower limit of sensitivity of 0.05 ng/ml, with an average inter- and intra-assay covariance of less than 15% and 8%, respectively. The assay sensitivity is based on the minimum DHEA-s concentration required to produce a two standard deviation from assay A0. DHEA-s data were converted to nmol/L (i.e., ng/ml $\times$ 2.71). The sample test volume for sAA was 10 μ l. Measurement units were expressed in nmol/L (ng/ml $\times$ 2.71). Original values without transformations were used for the analysis.

We summarized daily scores for each of the biomarkers, salivary cortisol ($n = 6,173$, 94.5% valid), DHEA-s ($n = 5,988$, 94.5% valid) and sAA ($n = 6,121$, 95.6% valid) based on valid

saliva samples. We computed daily total output for each observation day based on the existing formula for area under the curve with respect to ground (AUCg) [31]. The average daily total output (AUCg) was then calculated across the 8 days of observation at baseline and was used as the predictor of caregivers' longitudinal health trajectories for all three biomarkers.

Care transitions—Care transitions were determined during the 6-month and 12-month follow-up interviews. Based on their responses, caregivers who had placed their relative in an institution or turned the care over to another family member were coded as having a care transition ($= 1$ or, $0 = \text{did not have a transition}$).

ADS use—The total number of days that caregivers were having ADS per week at baseline was operationalized as the extent of respite intervention ($M = 3.89$ days, $SD = 1.15$ days).

Covariates—Additional variables from the baseline interview that are often associated with caregiver health were considered as covariates: caregiver age, relationship type ($1 = \text{spouse}$ and $0 = \text{other kin relationship}$), depressive symptoms [32] (depression subscale from the Non-Specific Psychological Distress Scale; 7 items on a 5-point scale ranging from $1 = \text{none of the day}$ to $5 = \text{all day}$; coded so that higher scores indicated more depressive symptoms; $\alpha = .81$), caregiving role overload (3 items on a 4-point scale ranging from $1 = \text{none of the time}$ to $4 = \text{all of the time}$; coded so that higher scores indicated more subjective experiences of being worn out and overloaded; $\alpha = .63$) [33], and caregiving role captivity (3 items on a 4-point scale ranging from $1 = \text{none of the time}$ to $4 = \text{all of the time}$; coded so that higher scores indicated that the caregiving role was unwanted; $\alpha = .83$) [33,34].

Analysis plan

The hypotheses were tested using three growth curve models for each of the three biomarkers with functional limitation over 12 months as the outcome. Hypothesis 1 on the associations between biomarkers and functional limitations in the context of care transitions was tested using a full model with main effects and interactions (*Model 1*). Specifically, Model 1 tested the main effect of care transitions and biomarkers on health change as well as the interactions between care transitions and stress biomarkers on health change. The level 1 equation in Model 1 and 2 was specified as:

$$\text{Health}_{ti} = \pi_{0i} + \pi_{1i} (\text{Time}_{ti}) + \varepsilon_{ti} \quad (1)$$

where caregiver health was modeled as a function of the intercept, the linear time, and the within-person residual term. Level 2 equations modeled the effects of daily stress biomarkers, and care transitions on caregiver health trajectories, while controlling for caregiver characteristics. Level 2 equations in Model 1 were specified as:

$$\begin{aligned}\pi_{0i} &= \beta_{00} + \beta_{01} (\text{Caregiver age}_i) + \beta_{02} (\text{Spouse caregiver}_i) + \beta_{03} (\text{Role overload}_i) + \\ &\quad \beta_{04} (\text{Role captivity}_i) + \beta_{05} (\text{Depressive symptoms}_i) + \beta_{06} (\text{daily stress biomarkers}_i) + \\ &\quad \beta_{07} (\text{Care transition}_i) + \nu_{0i} \\ \pi_{1i} &= \beta_{10} + \beta_{11} (\text{daily stress biomarkers}_i) + \beta_{12} (\text{Care transition}_i) + \beta_{13} (\text{daily stress biomarkers}_i) \\ &\quad \times (\text{Care transition}_i)\end{aligned}$$

(2)

where β s are population-level parameters; the person-specific intercept, π_{0i} , from equation (1) is now modeled as functions of average daily total outputs of cortisol, DHEA-s, sAA at baseline, and care transitions, while controlling for other caregiving characteristics; the person-specific linear time slope, π_{1i} , is also modeled as functions of average daily total outputs of cortisol, DHEA-s, sAA at baseline, care transitions, and the interactions between each of the daily total outputs of stress biomarkers and care transitions. ν_{0i} is between-person differences in the intercept with a variance, σ_v^2 . Model 1 tested the associations between functional health and each one of the biomarkers respectively, one at a time (Models 1.1, 1.2, and 1.3).

Next, to test Hypothesis 2 on ADS use, total ADS days per week at baseline were added to the model as an additional predictor in equation (2) (*Model 2*), while keeping the same level 1 equation as (1). Thus, the level 2 equations in Model 2 were specified as:

$$\begin{aligned}\pi_{0i} &= \beta_{00} + \beta_{01} (\text{Caregiver age}_i) + \beta_{02} (\text{Spouse caregiver}_i) + \beta_{03} (\text{Role overload}_i) + \\ &\quad \beta_{04} (\text{Role captivity}_i) + \beta_{05} (\text{Depressive symptoms}_i) + \beta_{06} (\text{daily stress biomarkers}_i) + \\ &\quad \beta_{07} (\text{Care transition}_i) + \beta_{08} (\text{Total ADS days}_i) + \nu_{0i} \\ \pi_{1i} &= \beta_{10} + \beta_{11} (\text{daily stress biomarkers}_i) + \beta_{12} (\text{Care transition}_i) + \beta_{13} (\text{Total ADS days}_i) + \\ &\quad \beta_{14} (\text{daily stress biomarkers}_i) \times (\text{Care transition}_i) + \beta_{15} (\text{daily stress biomarkers}_i) \times \\ &\quad (\text{Total ADS day}_i) + \beta_{16} (\text{Care transition}_i) \times (\text{Total ADS days}_i) + \beta_{14} (\text{daily stress biomarkers}_i) \times \\ &\quad (\text{Care transition}_i) \times (\text{Total ADS days}_i)\end{aligned}$$

(3)

where the person-specific linear time slope, π_{1i} , is now modeled as functions of total ADS days at baseline, daily stress biomarkers (i.e., average daily total outputs of cortisol, DHEA-s, and sAA at baseline), care transitions, and the interactions between these three terms. ν_{0i} is between-person differences in the intercept with a variance, σ_v^2 . Model 2 also tested the associations between functional health and each one of the biomarkers respectively, one at a time. All between-person covariates on demographics and caregiving characteristics were grand-mean centered.

Results

Hypothesis 1 was supported partially (Table 3, Model 1). Model 1 did not show any significant main effects. However, Model 1 showed that care transitions had significant interactions on the associations between functional limitation trajectory over 12 months and daily total outputs of all three biomarkers. Specifically, care transitions moderated the associations between functional trajectory and daily total output of cortisol ($\beta = -0.007$, $p < .0001$, Model 1.1), DHEA-s ($\beta = 0.002$, $p = .02$, Model 1.2), and sAA ($\beta = -0.0001$, $p = .0002$, Model 1.3), as indicated by three significant 3-way interactions in the models. Among caregivers who experienced a transition, lower cortisol daily total output (Figure 2), greater DHEA-s daily total output (Figure 3), and lower sAA daily total output (Figure 4) was associated with increasing functional limitations over time. Parameter estimates from Model 1 are presented in Table 3.

Next, Model 2 was fit to test Hypothesis 2 on the moderating effect of ADS use at baseline. The model showed that the extent of ADS use further modified the associations between functional limitation trajectory and daily total outputs of cortisol and sAA in the context of care transitions. First, the significant 4-way interaction in Model 2.1 ($\beta = 0.004$, $p = .013$, Table 4) showed that care transitions had an effect on the association between cortisol daily total output and functional trajectory, which in turn was modified by total ADS days. Specifically, among caregivers who experienced a transition, *and* who used less than average ADS days per week at baseline, lower daily cortisol total output was associated with increasing functional limitations (Figure 5 upper panel). Caregivers who experienced a transition but used greater than average ADS days per week did not show such patterns of association (Figure 5 upper panel). Second, the significant 4-way interaction in Model 2.2 ($\beta = 0.0001$, $p = .002$, Table 4) showed that care transitions had an effect on the association between sAA daily total output and functional trajectory, which in turn was modified by total ADS days. Specifically, among caregivers who experienced a transition, and who used less than average ADS days per week, lower daily sAA total output was associated with increasing functional limitations (Figure 5 lower panel). Caregivers who experienced a transition but used greater than average ADS days per week did not show such patterns of association (Figure 5 lower panel). No significant effect was found for DHEA-s. All significant findings from Models 2 are presented in Table 4. All models controlled for the same sets of covariates.

Discussion

This study is among the first to explore associations between daily biomarkers and long-term health among dementia family caregivers, and the moderating effects of care transitions and ADS use on such associations. The biological stress framework [1] and the caregiving stress process model [33] guided the study. Some of its strengths included the longitudinal measures on functional health, use of multiple biomarkers measured across days such that within-person variance was minimized, and the considerations of an intervention effect in the context of care transitions. We took into consideration factors that affected care-related stressor exposures, such as ADS use and giving up the caregiver role. Much of the longitudinal literature on caregivers overlooked the impact of care transitions, despite its

apparent implications for care-related stressor exposures and caregivers' daily experiences. Assessment of the association between stressors and health requires taking into account variances in stressor exposures over time. The study provided empirical evidence on the association between physiological regulation of stress and their health implications over time among dementia caregivers.

Biomarkers and health in the context of care transitions

The findings showed that although each of the stress biomarkers did not have significant main effects on functional health, trajectories of functional limitations over time were associated with daily stress biomarkers of both HPA and SNS in the context of care transitions. Prior studies examining associations between biomarkers and health change have used a much larger sample size, an index score based on multiple biomarkers, and performance-based measures on physical health such as balance and gait [35]. Possible explanations on null findings on the main effects of stress biomarkers on functional health include a relatively small sample, one type of stress biomarker reflecting HPA or SNS activity as the primary predictor, and self-reported functional status.

The findings on lower cortisol and sAA daily total outputs were consistent with previous studies on the allostatic load model of chronic stress and health problems [2]. Prolonged exposure to stress hormones such as cortisol can be detrimental, causing neuron loss in the brain and posing chronic health problems. Hypocortisolism and lower sympathetic activity may imply a potential physiological mechanism for increased susceptibility to functional declines [6,9]. Caregivers' deteriorating health can make providing care to a relative with dementia very challenging, making pre-mature care transitions a much more likely option when care receivers do not yet require care at such a level. The fact that the association between hypocortisolism, lower sAA levels, and increasing functional limitation was only pronounced among caregivers with transitions confirmed that physical health is an important resource for caregiving roles [27].

The finding on associations between greater DHEA-s levels and increasing functional limitations among caregivers who had transitions is a bit puzzling. Chronically stressed populations such as dementia caregivers typically have reduced DHEA-s levels than non-stressed controls [36]. As an antagonist to cortisol, existing research generally suggests that lower DHEA-s levels were associated with greater health risks such as cardiovascular disease and all-cause mortality [2,37]. Cross-sectional studies based on between-person associations also reported low DHEA-s values among women with poor functioning in daily activities [38]. Prior studies also suggested gender could be a contextual factor [39]. The fact that our sample consisted primarily of women caregivers may have contributed to the contradictory findings. However, it is not yet clear how DHEA-s would be associated with within-person changes in any health indicators over time, or whether self-reported functional limitation is a sensitive indicator for DHEA-s levels. More longitudinal studies are necessary to explore further the associations between DHEA-s, chronic stress, and health. Specifically, future studies need to consider the best way to integrate multiple stress biomarkers as predictors of objective measures of functional health over a longer period.

ADS use, caregiver health, and care transitions

The findings on ADS use extend the literature on its psychological and physical benefits for dementia caregivers [3,19]. There was an interesting finding on the extent of baseline ADS use on the biomarker-health association in the context of care transitions. Among caregivers who turned care over, the ones who had fewer ADS days per week at baseline seemed to show an association between low cortisol levels and increasing functional impairment over time. Such association was not pronounced among caregivers who had more ADS days and who also placed relatives. The same patterns also applied to daily sAA total output. The significant 4-way interaction between biomarkers, health change, total ADS days, and care transitions confirms prior findings on the health benefits of ADS use [3]. Similar to a medical drug, there appeared to be a dosage effect for ADS use. Specifically, more than average ADS days per week (average = 3.86 days) seemed to bring greater physical benefits and protection against functional impairment. This finding is consistent with the literature on health benefits of caregiving respite [17]. It is possible that higher levels of ADS use allow caregivers to spend more time on self-care in addition to reduced stressor exposure. Future research need to examine caregivers' time use, self-care activities, and well-being while their relatives attend ADS to elucidate the exact mechanism of its health benefits.

Limitations

There are some limitations in the study. First, there were only three measurement occasions on functional limitations over 12 months. A longer time span and more health dimensions are better to track longitudinal health changes as consequence of daily stress biomarkers. Second, biomarkers in the study were limited to neuroendocrine measures of SNS and HPA axis. To evaluate comprehensively the pre-disease pathways, biomarkers from other bodily systems are needed. Third, the sample of family caregivers in the current study is select in that they chose to use ADS at varying amount of days, and participated in both daily and longitudinal parts of the study. The sample size was relatively small, and consisted of primarily women caregivers. Therefore, we should use caution to generalize the current findings to other populations of caregivers, in spite of the interesting findings on biomarkers and health associations.

The findings have implications for ways to support informal caregivers through public policies. Family caregivers provide the predominant majority of care to persons with dementia as well as to persons with other types of disabilities. This voluntary care is an important contribution to the economy [40,41]. The value of family caregiving, however, has been largely unrecognized in policy making about the costs of long-term services and supports. The chronic stress of witnessing a close family member decline is painful; providing care under the enormity of such chronic stress can be detrimental to caregiver's well-being. Empirical studies have shown that caregiving respite such as ADS use can provide a predictable amount of relief to caregivers by lowering primary and care-related stressor exposures. The benefits of community-based ADS programs on caregiver health and well-being are therefore more realistic than hypothesized. However, states vary in the amount they cover ADS under Medicaid, so insurance coverage and hence potential out-of-pocket expenses may affect ADS use despite of its apparent health benefits for caregivers. How these programs may become part of the standard policy on routine caregiver support

will have important implications for caregiver well-being, and the quality of the nation's long-term services and supports system.

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References

1. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur J Pharmacol.* 2008; 583:174–185. [PubMed: 18282566]
2. Juster R-P, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev.* 2010; 35:2–16. [PubMed: 19822172]
3. Liu Y, Kim K, Zarit SH. Health trajectories of family caregivers: Associations with care transitions and adult day service use. *J Aging Health.* 2015; 27:686–710. [PubMed: 25348275]
4. Heim C, Ehler U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology.* 2000; 25:1–35. [PubMed: 10633533]
5. Epel ES. Psychological and metabolic stress: A recipe for accelerated cellular aging? *Horm.* 2009; 8:7–22.
6. Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychol Bull.* 2007; 133:25–45. [PubMed: 17201569]
7. Piazza JR, Almeida DM, Dmitrieva NO, Klein LC. Frontiers in the use of biomarkers of health in research on stress and aging. *J Gerontol Psychol Sci Soc Sci.* 2010; 65B:513–525.
8. Granger DA, Kivlighan KT, El-Sheikh M, Gordis EB, Stroud LR. Salivary α -amylase in biobehavioral research: Recent developments and applications. *Ann N Y Acad Sci.* 2007; 1098:122–144. [PubMed: 17332070]
9. Wolf JM, Nicholls E, Chen E. Chronic stress, salivary cortisol, and α -amylase in children with asthma and healthy children. *Biol Psychol.* 2008; 78:20–28. [PubMed: 18243483]
10. Singer, BH., Ryff, CD. *New Horizons in Health: An Integrative Approach.* Washington, DC: The National Academies Press; 2001.
11. Ghiciuc CM, Cozma-Dima CL, Pasquali V, Renzi P, Simeoni S, Lupusoru CE, Patacchioli FR. Awakening responses and diurnal fluctuations of salivary cortisol, DHEA-S and α -amylase in healthy male subjects. *Neuro Endocrinol Lett.* 2011; 32:475–480. [PubMed: 21876512]
12. Hellhammer J, Fries E, Schweisthal OW, Schlotz W, Stone AA, Hagemann D. Several daily measurements are necessary to reliably assess the cortisol rise after awakening: State- and trait components. *Psychoneuroendocrinology.* 2007; 32:80–86. [PubMed: 17127010]
13. Granger DA, Kivlighan KT, Blair C, El-Sheikh M, Mize J, Lisonbee JA, Buckhalt JA, Stroud LR, Handwerker K, Schwartz EB. Integrating the measurement of salivary α -amylase into studies of child health, development, and social relationships. *J Soc Personal Relationships.* 2006; 23:267–290.
14. Goldman N, Gleit DA. Sex differences in the relationship between DHEAS and health. *Exp Gerontol.* 2007; 42:979–987. [PubMed: 17604586]
15. Piazza JR, Charles ST, Sliwinski MJ, Mogle J, Almeida DM. Affective reactivity to daily stressors and long-term risk of reporting a chronic physical health condition. *Ann Behav Med.* 2013; 45:110–120. [PubMed: 23080393]
16. Pinquart M. Correlates of subjective health in older adults: A meta-analysis. *Psychol Aging.* 2001; 16:414–426. [PubMed: 11554520]
17. Zarit SH, Kim K, Femia EE, Almeida DM, Savla J, Molenaar PCM. Effects of adult day care on daily stress of caregivers: A within-person approach. *J Gerontol Soc Sci.* 2011; 66:538–546.

18. Zarit SH, Stephens MAP, Townsend A, Greene R. Stress reduction for family caregivers: Effects of Adult Day Care use. *J Gerontol Soc Sci.* 1998; 53B:S267–S277.
19. Zarit SH, Kim K, Femia EE, Almeida DM, Klein LC. The effects of adult day services on family caregivers' daily stress, affect, and health: Outcomes from the Daily Stress and Health (DaSH) study. *Gerontologist.* 2014; 54:570–579. [PubMed: 23690056]
20. Gitlin LN, Reeve K, Dennis MP, Mathieu E, Hauck WW. Enhancing quality of life of families who use adult day services: Short- and long-term effects of the Adult Day Services Plus program. *Gerontologist.* 2006; 46:630–639. [PubMed: 17050754]
21. Klein LC, Kim K, Almeida DM, Femia EE, Rovine MJ, Zarit SH. Anticipating an easier day: Effects of Adult Day Services on daily cortisol and stress. *Gerontologist.* 2016; 56:303–312. [PubMed: 24996408]
22. Leggett AN, Liu Y, Klein LC, Zarit SHVP. Sleep duration and the cortisol awakening response in dementia caregivers utilizing adult day services. *Heal Psychol.* 2016; 35:465–473.
23. Zarit SH, Whetzel CA, Kim K, Femia EE, Almeida DM, Rovine MJ, Klein LC. Daily stressors and adult day service use by family caregivers: Effects on depressive symptoms, positive mood, and dehydroepiandrosterone-sulfate. *Am J Geriatr Psychiatry.* 2014; 22:1592–1602. [PubMed: 24566240]
24. McCurry SM, Logsdon RG, Teri L, Vitiello MV. Sleep disturbances in caregivers of persons with dementia: Contributing factors and treatment implications. *Sleep Med Rev.* 2007; 11:143–153. [PubMed: 17287134]
25. Song Y, Washington DL, Yano EM, McCurry SM, Fung CH, Dzierzewski JM, Rodriguez JC, Jouldjian S, Mitchell MN, Alessi CA, Martin JL. Caregiving-related sleep problems and their relationship to mental health and daytime function in female veterans. *Behav Sleep Med.* 2016:1–12.
26. Gaugler JE, Kane RL, Kane RA, Clay T, Newcomer R. Caregiving and institutionalization of cognitively impaired older people: Utilizing dynamic predictors of change. *Gerontologist.* 2003; 43:219–229. [PubMed: 12677079]
27. Buhr GT, Kuchibhatla M, Clipp EC. Caregivers' reasons for nursing home placement: Clues for improving discussions with families prior to the transition. *Gerontologist.* 2006; 46:52–61. [PubMed: 16452284]
28. Stawski RS, Cichy KE, Piazza JR, Almeida DM. Associations among daily stressors and salivary cortisol: Findings from the National Study of Daily Experiences. *Psychoneuroendocrinology.* 2013; 38:2654–2665. [PubMed: 23856186]
29. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection *Med Care.* 1992; 30:473–483. [PubMed: 1593914]
30. Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD, McGlynn EA Jr, JEW. Functional status and well-being of patients with chronic conditions: Results from the medical outcomes study. *JAMA.* 1989; 262:907–913. [PubMed: 2754790]
31. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology.* 2003; 28:916–931. [PubMed: 12892658]
32. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SLT, Walters EE, Zaslavsky AM. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med.* 2002; 32:959–976. [PubMed: 12214795]
33. Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: An overview of concepts and their measures. *Gerontologist.* 1990; 30:583–594. [PubMed: 2276631]
34. Aneshensel, CS., Pearlin, LI., Mullan, JT., Zarit, SH., Whitlatch, CJ. Profiles in caregiving: The unexpected career. San Diego, CA: Academic Press; 1995.
35. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation — allostatic load and its health consequences: Macarthur Studies of Successful Aging. *Arch Intern Med.* 1997; 157:2259–2268. [PubMed: 9343003]
36. Moriguchi Jeckel CM, Lopes RP, Berleze MC, Luz C, Feix L, Argimon dL II, Stein LM, Bauer ME. Neuroendocrine and immunological correlates of chronic stress in 'strictly healthy' populations. *Neuroimmunomodulation.* 2010; 17:9–18. [PubMed: 19816052]

37. Shufelt C, Bretsky P, Almeida CM, Johnson BD, Shaw LJ, Azziz R, Braunstein GD, Pepine CJ, Bittner V, Vido DA, Stanczyk FZ, Bairey Merz CN. DHEA-s levels and cardiovascular disease mortality in postmenopausal women: Results from the National Institutes of Health — National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Clin Endocrinol Metab.* 2010; 95:4985–4992. [PubMed: 20739385]
38. Berr C, Lafont S, Debuire B, Dartigues J-F, Baulieu E-E. Relationships of dehydroepiandrosterone sulfate in the elderly with functional, psychological, and mental status, and short-term mortality: A French community-based study. *Proc Natl Acad Sci USA.* 1996; 93:13410–13415. [PubMed: 8917605]
39. Kudielka BM, Hellhammer J, Hellhammer DH, Wolf OT, Pirke K-M, Varadi E, Pilz J, Kirschbaum C. Sex differences in endocrine and psychological responses to psychosocial stress in healthy elderly subjects and the impact of a 2-week dehydroepiandrosterone treatment. *J Clin Endocrinol & Metab.* 1998; 83:1756–1761. [PubMed: 9589688]
40. Gibson MJ, Houser A. Valuing the invaluable: A new look at the economic value of family caregiving. Issue Brief (Public Policy Institute (AARP)). 2007:1–12.
41. Reinhard, SC., Feinberg, LF., Choula, R., Houser, A. Valuing the Invaluable: 2015 update - Undeniable progress, but big gaps remain. AARP Public Policy Institute; 2015.

Figure 1.
Conceptual model of the study

Figure 2.

Model predicted association between daily cortisol total output, care transitions, and functional limitation over time

Figure 3.
Model predicted association between daily DHEA-s total output, care transitions, and functional limitation over time

Figure 4. Model predicted association between daily sAA total output, care transitions, and functional limitation over time

Figure 5. Model predicted association between daily cortisol versus sAA total output, care transitions, total ADS days, and functional limitation over time

Table 1

Specific Care Transition Types at 6 and 12 Months

	6 Months	12 Months ^d
Caregiver with no care transitions ^a	135	119
Caregiver with a care transition ^{a,b}	37	53
Bereaved ^c	17	31
Nursing homes or assisted living	14	18
Turned care to another family member	3	0
Other types	3	3

Notes.

^aCare transition was dummy coded, which represented the *removal of caregiving* happened at either 6 months or 12 months (= 1, otherwise = 0) when the relative was still living and needed active care.

^b172 family caregivers participated at *least two waves* of data collection at baseline, 6 and 12 months. Two caregivers missed 6-month interview; three caregivers missed 12-month interview; 167 caregivers participated all three waves. The analysis did not include bereaved caregivers whose relatives passed away at either 6 months or 12 months ($n = 31$). The working sample of caregivers was $N = 141$.

^cTotal number of bereaved caregivers at either 6 or 12 months.

^dOne caregiver who institutionalized the relative at 6 month was missing the 12-month interview.

Table 2

Descriptives on Caregivers and Their Relatives (N = 141)

	<i>M or Freq</i>	<i>SD or %</i>
Age ^a	60.65	10.84
Female	133	86.90
Spouse	50	32.70
Child	94	61.40
Education ^b	4.38	1.18
Married with a partner	99	64.70
Depressive symptoms ^c	1.53	0.62
Duration of care ^d	62.67	46.27
Number of ADS days per week ^e	3.89	1.15
Relative's ADLs dependency ^f	3.00	0.50

Note.

ADS = adult day services; ADL = activities of daily living. The sample of caregivers participated at least two data collection at baseline, 6 and 12 months.

^a Age ranged from 39 to 89.

^b Measured on a 6-point scale: 1 (*less than high school*) to 6 (*post college degree*).

^c Measured as the mean of 7 items on a 5-point scale at baseline: 1 (*none of the day*) to 5 (*all day*).

^d Measured in months, and ranged from 2 to 216.

^e Number of ADS days per week ranged from 2 to 5.

^f Measured as the mean of 13 ADL items on a 4-point scale: 1 (*does not need help*) to 4 (*cannot do without help*), ranging from 2 to 4.

Table 3
The association between functional limitation trajectories and daily biomarkers in the context of care transitions

	Model 1.1 Cortisol	Model 1.2 DHEA-s	Model 1.3 sAA
Fixed effects			
Intercept	8.000 (0.244) ***	8.046 (0.251) ***	8.013 (0.243) ***
Time	0.007 (0.015)	0.003 (0.016)	0.007 (0.015)
Care transition	0.181 (0.658)	-0.439 (0.676)	-0.030 (0.651)
Average cortisol daily total output	-0.005 (0.005)		
Average DHEA-s daily total output		-0.001 (0.003)	
Average sAA daily total output			0.000 (0.000)
Time × care transition	0.009 (0.045)	0.150 (0.047) **	0.082 (0.042) *
Time × Average cortisol daily total output	0.000 (0.000)		
Time × Average DHEA-s daily total output		0.000 (0.000)	0.000 (0.000)
Time × Average sAA daily total output			
Time × care transition × Average cortisol daily total output	-0.007 (0.002) ***		
Time × care transition × Average DHEA-s daily total output		0.002 (0.001) *	
Time × care transition × Average sAA daily total output			0.000 (0.000) ***
<i>Covariates</i>			
Caregiver age	0.098 (0.028) ***	0.072 (0.028) *	0.067 (0.027) *
Spouse caregiver	-0.811 (0.574)	-0.537 (0.580)	-0.451 (0.562)
Depressive symptoms	1.074 (0.383) **	1.208 (0.404) **	1.210 (0.384)
Role overload	0.838 (0.341) *	0.707 (0.353) *	0.709 (0.340) **
Role captivity	-0.340 (0.299)	-0.531 (0.305)	-0.512 (0.297) *
Random effects			
Intercept VAR	4.795 (0.703) ***	4.828 (0.718) ***	4.601 (0.682) ***
Residual VAR	1.245 (0.130) ***	1.376 (0.145) ***	1.355 (0.142) ***
-2 Log Likelihood	1284.6	1272.3	1307.1
AIC, BIC	1288.6, 1294.3	1276.3, 1282.0	1311.1, 1316.8

Notes. All between-person covariates were grand-mean centered. AIC = Akaike information criterion; BIC = Bayesian information criterion.

.100[†] *d*

.10[†] *p*
**
.50[†] *d*
*

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ADS effect on the association between functional limitation trajectories and daily biomarkers in the context of care transitions

Table 4

	Model 2.1	Model 2.2
	Cortisol	sAA
Fixed effects		
Intercept	7.999 (0.240) ***	8.002 (0.248) ***
Time	0.006 (0.014)	0.008 (0.015)
Care transition	0.259 (0.650)	-0.014 (0.668)
Average cortisol daily total output	-0.006 (0.005)	
Average sAA daily total output		0.000 (0.000)
Total ADS days	0.051 (0.193)	0.088 (0.202)
Time × care transition	0.030 (0.044)	-0.010 (0.054)
Time × Average cortisol daily total output	0.000 (0.000)	
Time × Average sAA daily total output		0.000 (0.000)
Time × Total ADS days	-0.017 (0.012)	-0.023 (0.012)
Time × care transition × Average cortisol daily total output	-0.005 (0.002) **	
Time × care transition × Average sAA daily total output		0.000 (0.000) *
Time × care transition × Total ADS days	-0.055 (0.037)	-0.006 (0.053)
Time × Average cortisol daily total output × Total ADS days	0.000 (0.000)	
Time × Average sAA daily total output × Total ADS days		0.000 (0.000)
Time × care transition × Average cortisol daily total output × Total ADS days	0.004 (0.002) *	
Time × care transition × Average sAA daily total output × Total ADS days		0.000 (0.000) **
<i>Covariates</i>		
Caregiver age	0.099 (0.027) ***	0.062 (0.028) *
Spouse caregiver	-0.853 (0.573)	-0.495 (0.586)
Depressive symptoms	0.979 (0.377) *	1.144 (0.395) **
Role overload	0.937 (0.335) **	0.661 (0.350)
Role captivity	-0.364 (0.299)	-0.545 (0.309)
Random effects		
Intercept VAR	4.621 (0.679) ***	4.917 (0.732) ***

	Model 2.1	Model 2.2
	Cortisol	sAA
Residual VAR	1.158 (0.122) ***	1.240 (0.132) ***
-2 Log likelihood	1300.8	1344.9
AIC, BIC	1304.8, 1310.5	1348.9, 1354.6

Notes. All between-person covariates were grand-mean centered. ADS = Adult day services. AIC = Akaike information criterion; BIC = Bayesian information criterion. Total ADS days were measured at baseline as the total number of ADS days used per week.

*
p .05.
**
p .01.

p .001.