AGING, CAREGIVING, HEALTH AND WELL-BEING

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by
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ABSTRACT

Providing care for an older relative with dementia has been found to be highly stressful, and the caregiving experience may erode caregivers’ psychological well-being as well as physical health (Aneshensel, Pearlin, Mullan, Zarit, & Whitlatch, 1995). In this dissertation, I propose to explore the consequences of family caregiving as pertain to caregiver health and well-being at both the within and between-person levels.

The dissertation compiles three studies that utilize data from the Daily Stress and Health (DaSH) Study. DaSH has a within-person single-group design using daily diary methods with 184 caregivers. At baseline, there was an in-person at-home interview, followed by 8 dairy days. Caregivers filled out daily dairies on these 8 consecutive days; they were also interviewed by phone in each of the 8 evenings to report their daily experiences. On some of the dairy days, the individual with dementia (IWD) was attending day care; and on the rest of them, the caregiver was actively caring for the IWD. Saliva samples were collected 5 times on each diary day; these samples were used to test for levels of 3 hormones related to the stress process: the cortisol, DHEA-s, and alpha-amylase. Each hormone was hypothesized to have unique implications for caregiver health. Patients’ behavior stressors were also reported each day for 4 time periods, which corresponded to the timing of Adult Day Services (ADS) use. There were two longitudinal follow-up interviews by telephone: at 6 month and 12 month that assessed the caregivers’ continuing ADS use, health, and well-being.

The three studies examine the effects of stress on affect, health, and biomarkers in a sample with high levels of daily stressors; they also examine how an intervention, ADS use, that changes daily stressor exposures influences caregivers’ daily health and well-being. Study 1
examines three spline growth models fit to daily cortisol levels, and the effect of ADS use on diurnal cortisol regulations in the daily caregiving context. Study 2 examines the typical diurnal trajectory of salivary alpha-amylase (sAA) using a piecewise linear spline model. It also examines the effect of ADS use on diurnal sAA regulation in the context of daily experiences. Last, study 3 uses growth curve models to explore the association between caregivers’ daily stress biomarker responses and their long-term health. This study incorporates data collected using different time scales, and uses multiple health indicators and biomarkers. It explores the moderating effects of ADS use and caregiving transitions on the biomarker-health associations.

Overall, the findings suggest the subtleties of health disparity among caregivers of IWDs. Further, ADS use is effective in containing the chronic stress and physiological toll of caregiving on a daily basis and over time. The studies provide some scientific evidence for promoting caregiving respite programs.
# TABLE OF CONTENTS

LIST OF TABLES........................................................................................................................................... vi
LIST OF FIGURES............................................................................................................................................ vii
ACKNOWLEDGEMENTS................................................................................................................................. viii

Chapter 1. INTRODUCTION............................................................................................................................... 1
   1.1 Overview of the Problem............................................................................................................................ 1
   1.2 Background and Literature Review......................................................................................................... 2

Chapter 2. STUDY 1: Modeling Daily Cortisol Rhythms of Family Caregivers of Individuals with Dementia: Daily Stressors and Adult Day Services Use
   2.1 Background and Literature Review........................................................................................................... 23
   2.2 Methods................................................................................................................................................... 29
   2.3 Results.................................................................................................................................................... 39
   2.4 Discussion............................................................................................................................................... 41
   2.5 Tables and Figures.................................................................................................................................... 47

Chapter 3. STUDY 2: Diurnal Salivary Alpha-amylase Dynamics among Dementia Family Caregivers: Daily Stressors and Adult Day Services Use
   3.1 Background and Literature Review........................................................................................................... 54
   3.2 The Current Study.................................................................................................................................... 59
   3.3 Methods.................................................................................................................................................. 60
   3.4 Results.................................................................................................................................................... 67
   3.5 Discussion............................................................................................................................................... 69
   3.6 Tables and Figures.................................................................................................................................... 74

Chapter 4. STUDY 3: Linking Daily HPA and SNS Activity to Family Caregiver Health over Time: Caregiving Transitions and Adult Day Services Use
   4.1 Background and Literature Review........................................................................................................... 80
   4.2 The Current Study.................................................................................................................................... 86
   4.3 Methods.................................................................................................................................................. 87
   4.4 Results.................................................................................................................................................... 93
   4.5 Discussion............................................................................................................................................... 94
   4.6 Tables and Figures.................................................................................................................................... 98
   4.7 Appendix................................................................................................................................................ 109

Chapter 5. CONCLUSION................................................................................................................................. 110

REFERENCES.................................................................................................................................................... 116
LIST OF TABLES

Table

1. Descriptive statistics for salivary cortisol……………………………………………………47
2. Salivary cortisol levels and associations with daily experiences and caregiving characteristics………………………………………………………………………………48
3. Model comparison among three unconditional spline models on cortisol diurnal trajectory…………………………………………………………………………………49
4. Effect of ADS use on diurnal cortisol slopes covarying for daily experiences and caregiving characteristics using linear spline mode………………………………………50
5. Daily salivary alpha-amylase sample descriptives……………………………………………………74
6. Associations between salivary alpha-amylase levels, daily experiences, and caregiving characteristics…………………………………………………………………………………75
7. Effect of ADS use on diurnal salivary alpha-amylase slopes covarying for daily experiences and caregiving characteristics……………………………………………………76
8. Caregivers’ Characteristics at Baseline (N = 165)………………………………………………98
9. The association between health trajectories and daily biomarkers in the context of caregiving transitions………………………………………………………………….99
10. ADS effect on the association between functional limitation trajectories and daily biomarkers in the context of caregiving transitions……………………………………101
LIST OF FIGURES

Figure

1. Diurnal salivary cortisol curves based on the three unconditional models………………52
2. The effect of daily ADS use on salivary cortisol diurnal slopes…………………………53
3. The typical diurnal alpha-amylase trajectory among dementia family caregivers………78
4. The association between total ADS days and alpha-amylase diurnal slopes…………….79
5. Conceptual model of the study………………………………………………………………………103
6. Changes in functional limitation and daily cortisol total output…………………………104
7. Changes in functional limitation and daily DHEAs total output…………………………105
8. Changes in functional limitation and daily sAA total output……………………………106
9. Changes in functional limitation and cortisol daily total output for caregivers who had lower versus higher than average ADS days per week…………………………………107
10. Changes in functional limitation and sAA daily total output for caregivers who had lower versus higher than average ADS days per week……………………………………108
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CHAPTER 1. INTRODUCTION

1.1 Overview of the Problem

With the changing demographic landscape of society, people live longer with the major burden of illness being chronic diseases (Fries, 1980, 2005). Thanks to the modern medical advances, impaired elders survive with disabilities for longer periods of time in spite of their health problems. Because of many barriers to suitable institutional care, such as the cost and often elusive quality, most families are committed to caring for their impaired relatives at home. Family care, usually to the patients’ advantage, takes a toll on the caregivers. Providing care for a frail elder has been found to be stressful, and the caregiving experience may erode caregivers’ psychological well-being as well as physical health (Aneshensel, Pearlin, Mullan, Zarit, & Whitlatch, 1995). Some caregivers continue to provide home care for years and even decades, long after their resolve and physical well-being has been worn down. As suggested by many cross-sectional findings, providing informal care to loved ones may exacerbate the normal aging processes observed among ordinary individuals.

In this dissertation I will suggest that consequences of family caregiving as pertain to caregiver health and well-being is nevertheless a varying phenomenon. Many subtleties of health disparity among caregivers can be better modeled and presented using assessment designs combining both micro and macro time scales and incorporating biomarkers of stress and health. All three papers will utilize data from the Daily Stress and Health Study (DaSH). Study 1 examines three spline growth curve models fit to daily cortisol levels, and the effect of adult day services (ADS) use on cortisol diurnal regulation in the daily context. Study 2 explores the diurnal trajectory of salivary alpha-amylase (sAA), and examines the effects of ADS use and daily stressor exposures on sAA diurnal regulations. Finally, Study 3 incorporates different time
scales and links daily stress biomarker responses to caregivers’ long-term health. In this introduction chapter, a general review of health and well-being among family caregivers of people with disability is presented, followed by a discussion of the rationale to examine different biomarkers and the biobehavioral model to study caregiver health and well-being. Particular emphasis is placed on the appropriate methods to better study health.

1.2 Background and Literature Review

Caregiver Health and Well-being in General

Pinquart and Sörensen (2003b) conducted a meta-analysis based on findings from 84 published studies on differences between caregivers and non-caregivers in various aspects of health and well-being. Caregiving were operationalized as someone providing informal care to an elderly relative with chronic physical and/or cognitive impairments. The average age of a caregiver was 62.5 (sd = 8.6 years), and the average age of a care recipient was 75.6 (sd = 4.4 years). The types of illness reviewed that required for care included dementia, cancer, stroke, and others. Physical health was measure by a single item on general health perception among 18 evaluated studies. The authors found that caregivers had greater stress and depression, lower levels of subjective well-being, lower self-efficacy, and poorer physical health than non-caregivers. However, differences of physical health, between caregivers and non-caregivers were smaller than other health and well-being outcomes, although significant. The strongest detrimental effects of caregiving were found in depression.

Caregiving to a relative afflicted with dementia has been considered more challenging compared to other types of chronic conditions, as consequence of the degenerative nature of the disease (Pearlin, Mullan, Semple, & Skaff, 1990). When disease types were considered, Pinquart and Sörensen (2003b) found the differences in psychological and physical health in
favor of non-caregivers were larger in studies with only dementia caregivers, although still significant in the combined diseases groups. Specifically, there is a tendency for dementia caregivers to be more depressed than non-caregivers. The findings of dementia caregiving were observed even after all other caregiving characteristics and study characteristics were controlled.

If we consider studies incorporating physiological measures as well as self-reports of dementia caregiver health, strong negative effects of caregiving are found in stress hormones, antibodies, and global reported health (Vitaliano, Zhang, & Scanlan, 2003). Caregivers had more health problems and greater potential illness risks than non-caregiver matches for age and gender; caregivers also had a 23% higher level of stress hormones and 15% lower level of antibody responses than did non-caregivers. Given that these physiological measures can show pre-disease pathways much earlier before the actual illness onset, the potentially added risks may have important clinical implications for caregivers, especially the vulnerable subgroups of caregivers who have comorbidities (Navaie-Waliser et al., 2002; Vitaliano et al., 2003).

Longitudinal studies have shown different findings on caregiving and well-being and health. One of the first longitudinal studies showed a decline in spouse caregivers’ subjective burden after 2 years for both caregivers who had been providing active in-home care and those who had placed their relatives in nursing homes (Zarit, Todd, & Zarit, 1986). However, a study of daughter caregivers for parents with diverse health needs showed a nonsignificant decline in depression with substantial individual differences over an 18-month period (Li, Seltzer, & Greenberg, 1999). Similarly, a study on older husbands caring for wives with functional and/or cognitive impairments showed stability over one year at the group level, in relation to psychological distress and global health (Ducharme, Lévesque, Zarit, Lachance, & Giroux, 2007). Further, in a study examining changes in mental and physical health with the transition
into caregiving roles, Lawton and colleagues (2000) did not find any significant changes in new caregivers’ quality of life, or any detrimental effects on health as measured by health conditions and general health perceptions over one year. Focusing on physical health symptoms, Goode and colleagues (1998) found dementia caregivers had stable physical health over time. Nevertheless, Baumgarten and colleagues (1994) found that caregivers were more likely to experience an increase in depression and physical symptoms over one year, although the increase was not significant.

To sum, cross-sectional findings generally show that, compared with non-caregivers, caregivers are more stressed, depressed, have lower levels of subjective well-being, worse physical health, and lower self-efficacy (Aneshensel et al., 1995; Mausbach, Chattillion, Roepke, Patterson, & Grant, 2012; Mausbach, Roepke, et al., 2012; Pinquart & Sörensen, 2003a, 2003b). However, greater senses of mastery and positive coping strategies may reduce the physiological reactions to caregiving stress, and benefit physical health in the long run (Harmell, Chattillion, Roepke, & Mausbach, 2011). Additionally, the size of the differences between caregivers and non-caregivers in relation to the above outcomes was medium to small. However, longitudinal studies have shown relatively stable health and well-being in relation to caregiving, with individual differences in patterns of change over time. Since there are a substantial proportion of caregivers who manage the daily challenges well, and experience few negative effects, if any, as a consequence of caregiving, caregiving is not a uniformly aversive experience. It would be important to consider disease types, caregiving tasks, specific caregiving stressors, caregiver resource and support, positive aspects of caregiving, and other caregiver demographics.

Factors Associated with Caregiver Health and Well-being: Cross-sectional Studies
Some caregiving characteristics are associated with caregivers’ impaired psychological well-being, such as gender, age, ethnicity, caregiver-patient relationship types, and psychosocial resources of social support and mastery. In general, negative caregiving outcomes were more pronounced in female caregivers: females were more depressed, had more burden, and performed more caregiving tasks, although the gender differences were quite small (Pinquart & Sörensen, 2006). Although women may be more socialized to provide care, caregiving may bring role conflicts especially for middle-aged women who are employed, and are parents of younger dependents. For older women, caregiving to husbands may be resented because some of them look to their later years as a time for personal growth and relaxation (Zarit et al., 1986). Also, older caregivers were more likely to have higher levels of depression, increased stress, and lower levels of self-efficacy (Pinquart & Sörensen, 2003b). Further, caregiving may have different effects for caregiver with distinctive ethnicities. Pinquart & Sörensen (2005) found that Hispanic and Asian-American caregivers were more depressed than the non-Hispanic Whites; and Whites had better physical health than all groups of ethnic minority caregivers.

Caregiver-patient relationship type may also qualify the caregiving outcomes. Pinquart & Sörensen (2011) found that spouse caregivers provided more care, had greater financial and physical burden, were more depressed, and had lower psychological well-being. There are several theoretical explanations for heightened distress in spouse caregivers. Spouses have the closest relationships to the patients, and the closer relationships are often associated with more caregiving distress (Cantor, 1983). The interpersonal effects of suffering in older adult caregiving dyads show that the exposures to patients’ physical symptoms and emotional distress have a direct impact on caregivers’ emotions in that they experience similar negative emotions, possibly through empathy (Monin & Schulz, 2009). In addition, spouses are likely to coreside
with care receivers, thus they tend to provide more care and often find little respite from the constant caregiving demands. Further, spouse caregivers tend to be older compared with adult-children caregivers, and may have more chronic conditions and functional limitations, and have more difficulty managing the care. On the other hand, there are reasons for spouse caregivers to be in a better position for having reduced caregiving distress. Spouses are less likely to experience role conflicts than adult children, and are less likely to provide sandwich care. Also, spouses tend to have intrinsic motivations toward caregiving, regarding it as an extension of care and love; whereas adult children tend to have extrinsic motives stemming from duty and filial responsibilities, increasing their psychological distress (Pinquart & Sörensen, 2011).

Coping resources like social support and mastery or self-efficacy may constrain the stress process, indirectly reducing the risks of deleterious outcomes of caregiving. Pearlin and colleagues considered social support to be: “the access to and use of individuals, groups, or organizations in dealing with life’s vicissitudes” (Pearlin, Menaghan, Morton, & Mullan, 1981) p.340. The authors indicated that a support system does not necessitate the existence of a social network, although the network can be a first step to draw on social relations for support. Having access to support depends on the quality of the relations one has with the network, which may involve exchange of intimate communications and the presence of solidarity and trust. Two functional components of social support usually considered in caregiving are socio-emotional support and instrumental support, which can be informal or formal (Aneshensel et al., 1995). Another type of resource, which is considered personal rather than social, is mastery or self-efficacy. Mastery refers to “the control individuals feel they are able to exercise over forces importantly affecting their lives” (Aneshensel et al., 1995) P.154.
Studies show that psychosocial resources have independent effects on various caregiving outcomes, and they appear to be antecedent to some care-related stressors, rather than consequences; these effects are, in general, beneficial. Aneshensel and colleagues (1995) found, however, that greater instrumental support from family and friends with patient care at an earlier time were associated with increasing amounts of role overload and captivity later; instrumental support in general did not contain care-related stressors, nor did it influence the timing of nursing home placement. Additionally, the resource that seems to matter most to the constraint of subjective stressors is caregivers’ personal mastery: a strong sense of mastery was associated with lower role overload, role captivity, and less loss of intimate exchange. Lower levels of mastery were also associated with worse depressive symptoms (Li et al., 1999).

Several factors specific to the caregiving context such as the degree of patient impairment, caregiving tasks or involvement, and positive aspects of caregiving are also associated with caregiver burden and depression based on cross-sectional findings. To start with, these factors are not entirely independent from each other, and a small to medium correlations exist between objective primary stressors and caregiving tasks/involvement (Aneshensel et al., 1995). The average correlations between cognitive/physical impairment, problem behaviors, hours of care and numbers of caregiving tasks ranged between .15 and .43, whereas positive aspects of caregiving were inversely correlated with problem behaviors as well as hours of care provision (Pinquart & Sörensen, 2003a).

Turning to the associations between caregiving characteristics and caregiver burden and depression: greater burden and depression were associated with more patient problem behaviors, more hours of care per week, and longer duration of caregiving, controlling for the inter-correlations between patient impairment and caregiving involvement. Additionally, more
Caregiver burden but not depression was related to more caregiving tasks and greater physical impairment of the patient; more caregiver depression was related to greater patient physical and cognitive impairment (Pinquart & Sörensen, 2003a). Pinquart & Sörensen (2003a) showed that the observed associations vary depending on caregiver-patient relationship types. There was a stronger association between burden and patient physical impairment and problem behavior for spouses than adult children; and a positive association between caregiver burden and duration of care in spouses only. The associations were stronger in probability samples than in convenience samples and stronger among dementia caregivers than caregivers with heterogeneous disease types. For dementia caregiving specifically, more caregiver burden was closely related to more hours of care provision and fewer self-reported positive aspects of caregiving.

Caregivers’ physical health is associated with a number of individual and contextual factors. In general, poor physical health was more strongly associated with subjective distress (e.g., feelings of burden) than with objective stressors (e.g., IWDs’ behavior problems or cognitive impairment). Caregivers in poor health were more likely to be older, married, less educated, unemployed, and assisting their relatives with basic PADL and IADL needs like bathing, dressing, and managing finances (Navaie-Waliser et al., 2002). Further, worse physical health of caregivers was associated with longer caregiving durations, co-residence with care recipients, and fewer caregiving tasks (Pinquart & Sörensen, 2007). Caregivers who had fair to poor health, or who had a serious health condition were likely to report their health suffered as a result of caregiving, to have unmet needs in providing care, and to have difficulties in managing daily caregiving responsibilities. Pinquart and Sörensen (2007) indicated that performing more caregiving tasks was associated with better caregiver physical health, although it was also related to higher burden. This “suppressor” effect shows that after ADL dependency of IWDs is
accounted for, caregivers with better health are able to meet higher demands of caregiving responsibility and provide higher levels of support.

Psychosocial resources and caregiving characteristics are not independent, and indeed are related to each other. Li and colleagues (1999) found that mastery has an inverse relationship with caregiving responsibilities/tasks, such than daughter caregivers in their study had lower levels of mastery when they had additional caregiving demands. Instrumental support from siblings, however, had a positive effect on mastery, such that when caregiving was shared with siblings, daughter caregivers had higher levels of mastery compared with those without the support. The authors also found that mastery was higher among caregivers who had better education, and better physical health. Additionally, caregivers with higher levels of mastery were more likely to use positive coping strategies with a problem-solving focus; whereas caregivers with lower levels of mastery tended to use emotion-focused coping strategies.

Factors Associated with Caregiver Health and Well-being: Longitudinal Studies

Longitudinal findings echo several themes of findings from the cross-sectional studies, but they depict a slightly different picture of factor associations with caregiver health and well-being. Some of the most frequently studied covariates are gender, caregiver-patient relationship type, psychosocial resources (social support, coping, and mastery), objective and subjective primary stressors of caregiving, caregiving transitions, and other caregiver demographic variables; the most common caregiver outcomes are changes/trends of caregiver burden, depression, and global health. Most of the studies treated the caregiving characteristics as time-invariant covariates, and considered caregiver outcomes at multiple time points.
In one of the first caregiver longitudinal studies, Zarit and colleagues (1986) studied changes in spouse caregivers’ burden, and associations with institutionalization of patients with dementia. At the group level, there was a decreasing trend of patient problems behaviors, as well as reduced caregiver burden. However, for caregivers who were still providing active in-home care at follow-up, although their perceived emotional support increased, their instrumental support decreased. The trajectories of subjective burden were different for wife/women vs. husband/men caregivers. Wives reported more burden than husbands at baseline, but no between-group differences were found at the follow-up over two years. Wives experienced significant decreases in burden over time, however, and the magnitude of decrease was especially large for the wives who had high burden at baseline, and who placed their spouses between the baseline and follow-up interviews.

In one of the first longitudinal studies on changes in caregiver physical symptoms, Baumgarten and colleagues (1994) found there was stability over one year in caregiver depression and physical symptoms at the group level. At the subgroup level, however, depressive symptoms increased in caregivers who were exposed to higher levels of problem behaviors, and who placed their relatives into a nursing home during the study period. Also, caregivers who institutionalized their relatives were more likely to experience a significant increase in physical symptoms. The authors then concluded that increased physical health problems in caregivers were more likely to be the antecedent, rather than consequence of patient institutionalization.

Li and colleagues (1999) examined changes in daughter caregivers’ depressive symptoms over 18 months and associations with coping, caregiving demands, and social support. Care receivers in that study were aging parents with diverse care needs, including dementia, heart
disease, stroke, arthritis, diabetes, and others. The authors found that emotion-focused coping was associated with worsening depression between baseline and the follow-up; whereas coping with a problem-solving focus was associated with decreasing levels of depression during the study period. Moreover, patient problem behaviors or other caregiving responsibilities were not found to be associated with changes in caregiver depressive symptoms. Also, instrumental support from siblings was related to changes in caregiver depression, such that caregivers who had the support at baseline reported decreasing depression at follow-up.

In a similar vein, Goode and colleagues (1998) examined changes in dementia caregiver depression and physical symptoms over one year, and associations with the primary stressors and psychosocial resources of appraisals, coping styles, and social support. Patients had increasing memory and behavior problems over the study period; however, these primary stressors did not directly predict any increase in caregiver depression or decline in physical health at the group level. Furthermore, the increase in patient memory and behavior problems predicted the increase in caregivers’ stress appraisals, which in turn predicted the increase in caregiver physical symptoms and depression. This suggested the mediating effect of stress appraisals on caregiver health and well-being. Still in the context of increasing patient memory and problem behaviors, initial levels of positive coping and total social support had protective effects on changes in health symptoms. This suggested the moderating effect of positive coping and total social support on caregiver health and well-being.

Mausbach and colleagues (2007) examined the moderating effect of mastery on the relations between caregiving stressors (role overload) and caregiver depression and physical health over five years. Caregiver’s personal mastery was measured across time; however, it showed stability during the study period. Thus, the baseline measure was used as the covariate.
The study showed that when baseline mastery was low, there were significant within-person covariations between role overload and depression, and role overload and physical symptoms. These findings showed the protective effect of mastery: a strong sense of mastery may initiate positive coping, enabling caregivers to take an active problem-focused approach toward objective primary stressors; such a positive coping strategy may also reduce negative coping. On the other hand, positive coping can constrain the initiation of some patient problem behaviors, ameliorating some of the objective stressors in caregiving. Similarly, Romeo-Moreno and colleagues (2012) examined effects of a number of time-varying covariates on elderly family caregivers’ depression over one year. They found that increases in caregivers’ self-efficacy, leisure activities, and use of cognitive reappraisal (the “cognitive ability to change thoughts in a positive way in order to repair unpleasant moods”, p. 1319) were predictive of decreasing depression over time, whereas increases in objective primary stressors were associated with worsening depression in the long run. These time-varying covariates are considered as resources in caregiving, and the longitudinal findings verified the ones reported based on cross-sectional studies.

Finally, Aneshensel and colleagues (1995) examined the effect of psychosocial resources on five dimensions of caregiver well-being: role overload, captivity, role strains, secondary intrapsychic strains, and depression. Several main findings are worth mentioning. Over the short term of one year, mastery and instrumental support are key contributors to stress that influence depression trajectories over time. First, a consistently strong senses of mastery tended to be associated with decreasing depression; and strong mastery tended to reduce subjective primary stressors (role overload, captivity, and loss of intimate exchange with the patient), which in turn lead to better emotional well-being. Second, instrumental support with
patient care affected caregiver depression directly and indirectly in a more complex way. Instrumental support directly decreased caregiver depression over time; whereas receiving family and friends’ assistance with patient care tended to increase subjective stressors of overload and captivity, which indirectly elevated caregiving depression. Over the long term of three years, caregivers who have an increasing sense of mastery tended to experience less role captivity over time; those who have consistent socioemotional support tended to feel less captive in the caregiving role. Role captivity tended to covary with caregiver depression over time. Both mastery and socioemotional support were protective of caregivers’ sense of personal identity; and mastery was protective of caregiver depression. Caregivers who have consistent informal support tended to be less depressed over time, whereas those who needed such help but do not receive any over time were more depressed.

Implications of Differences in Findings between Cross-sectional vs. Longitudinal Approaches

Finding from empirical research have practical implications for intervention efforts to help manage the care at home, and help enhance caregivers’ well-being and health; they may also assist theoretical refinement and development. While cross-sectional studies show, in general, the detrimental effects of caregiving, these negative images associated with caregiving are not completely reflected in the longitudinal studies, which show rather diverse patterns of within-person changes in the health domains. This difference suggests that, compared with non-caregivers, caregivers are exposed to greater stressors, which makes them vulnerable to psychological distress and physical ailment. Thus, caregiver interventions are quite necessary and important to promote caregiver well-being. On the other hand, the ideal interventions should be primary prevention (not secondary or tertiary), targeting at health and wellness promotion before serious psychological and health problems emerge.
First, caregivers are not sick or unhealthy. In fact, many of them are relatively healthy to assume the caregiving role (McCann, Hebert, Bienias, Morris, & Evans, 2004). Thus, to lower depressions should not become the direct treatment goal of the proposed primary caregiver interventions (Zarit & Femia, 2008). However, it is assumed that caregiving role is new for some caregivers, and they may have inadequate knowledge about their relatives’ disease or how best to accommodate their relatives’ daily needs, while still leading a fulfilling life themselves. Therefore, the primary goals of an intervention need to focus on the common vulnerabilities observed in caregiving: a) To make caregiving more manageable; b) To promote positive views and beliefs toward care provision, emphasizing caregiving as the extension of care and love, and experiences of giving back and personal growth (vs. being preoccupied with negative images of caregiving: stressful, unwanted, and detrimental to personal well-being); and c) To promote positive caregiving relationships by best maintaining IWDs’ functions, establishing a routine for caregivers’ self-care, easing communication between the caregiving dyads and other family members, creating positive emotional experience, and adopting a problem-solving and positive coping strategy. Such intervention may have the following secondary goals: a) To make caregiving more sustainable; b) To minimize caregivers’ negative emotionality with regard to caregiving experience; c) To minimize caregivers’ and IWDs’ physical declines. Based on the primary and secondary goals, the intervention’s ultimate goals are: a) Better quality of life for both caregivers and patients; and b) delayed patient institutionalization.

Second, significant within-person variation in patterns of change over time suggested that caregiver interventions must pay special attention to individual caregivers; program components should address person-specific needs, taking into account the specific caregiving situations, and the individual profile of resource and vulnerability. Thus, individualization is the key to
caregiver interventions. The National Research Council suggested that the next generation of interventions need to be multi-component, adaptive, and dynamically tuned to obtain optimal outcomes (Singer & Ryff, 2001). This approach means that caregiver intervention programs need to have multiple basic components based on the common vulnerabilities observed in both cross-sectional and longitudinal studies. Potential intervention components may include caregiving respite, caregiving counseling and support, and physical health promotion. However, at program in-take, each caregiver may adopt different combinations of intervention components, based on their specific caregiving needs and vulnerabilities. Over the course of intervention, caregivers need to be evaluated frequently to adjust their program package according to the changes in the risk profile. These strategies will make such intervention adaptive to the most recent caregiving needs.

On the one hand, findings from cross-sectional studies have helped the gradual evolvement and refinement of the stress process model, which have in turn guided caregiving research (Pearlin et al., 1981; Pearlin et al., 1990; Zarit, 1989; Zarit, Reever, & Bach-Peterson, 1980). The predominant caregiving research so far, however, is at the between-person level. Because of the immense difference between the between-person vs. within-person approaches to study development, health and well-being (Molenaar, 2004), more caregiving studies at the within-person level combining intensive and traditional longitudinal designs are still needed to further verify and refine the stress process model. The refinement of caregiving theory and accumulating empirical findings from new longitudinal studies will help develop intervention programs that make the heroic endeavor of caregiving more manageable and sustainable, and, at the same time, promote caregiver health and well-being.

*The Need to Study Biomarkers of Health and Well-being*
As Selye (1976) put it almost four decades ago: “It is only by the intensity of its manifestations – the adrenal enlargement, the increased corticoid concentration in the blood, the loss of weight, and so forth – that we can recognize the presence and gauge the intensity of stress.” Biological mechanism is one way of stress manifestation, which can be reliably detected and measured. Such processes may be the underlying mechanism between stressor exposures and long-term health and well-being.

The Pre-disease Pathways. The concept of pre-disease pathways describes the biological influences and associated links to behavioral, psychological, and social influences that extend way before the onset of diseases and mortality (Singer & Ryff, 2001). A more distant time point to disease onset is necessary to facilitate understanding about links between early antecedents to later risk factors; and the etiological processes leading to disease outcomes. The pre-disease pathways embrace a broad range of factors that impact individuals throughout the entire human developmental processes. Such influences include prenatal and early life risk factors (i.e., mothers’ health behaviors during pregnancy and parenting), psychosocial factors (i.e., optimism and emotional regulation), behavioral factors (i.e., diet and physical activity), and influences from the family and broader community and social environment (i.e., family support and social value).

Further, based on the theme of integrative research, risk/protective factors across multiple systems need to be assessed simultaneously. Chronic underexposure to protective factors and repeated exposure to challenge can disrupt biological regulations central to physiological homeostasis and health. Exposures to risks at critical and vulnerable developmental times early in life, and repeatedly in later periods of life can tax the physiological systems, making the responses operate abnormally. This cumulative physiological risk exacts wear and tear on
humans over time. How to optimally operationalize such risk across bodily systems over time will have implications on characterization of pre-disease pathways. One emerging direction of study on cumulative physiological risk is the allostatic load, which shows the impact of interactions between psychosocial factors, behavioral factors, and environmental influences on humans. Thus, to focus on pre-disease pathways, there is the need to identify early biomarkers of pre-disease states, to identify behavioral risk/protective factors that exacerbate or ameliorate pre-disease pathways, to conduct longitudinal studies to examine dynamic processes and differential trajectories across the life span with different time frames, and to examine an array of precursors (biological, behavioral, and psychosocial) to disease simultaneously.

Positive Health. While a predominant amount of research efforts has been allocated to study health as the absence of disease, researchers tend to forget a critical counterpoint to understanding pathways to illness, that is, positive health and the presence of wellness. Similar to the study of absence of illness, an understanding of the etiology and promotion of positive health outcomes includes examining resilience and resistance to disease processes, recovery and differential survival from illness. Primary prevention and positive health promotion will be the main routes to extend disability-free years and maximize quality of life.

Maintaining positive health has to do with a multitude of factors at the biological, behavioral (i.e., good health practices), psychosocial (i.e., purpose and meaning, sense of mastery, and positive affect), and environmental levels (i.e., positive value, community support) (Singer & Ryff, 2001). Particularly, there is a pressing need to explicate the biological substrates of the different factors, and their specific functions in pre-disease processes. Specifically, studies need to focus on the neurobiological mechanisms (i.e., allostasis and its variations, and anabolic and catabolic systems in response to challenges) between pro-health factors (i.e., nutrition,
physical activity, emotional well-being) and positive health outcomes; the science of primary intervention to overcome risk factors (i.e., maladaptive behaviors like sedentary lifestyles and avoidance coping), and promote protective factors (i.e., positive stress management, and balanced diet).

**Allostasis and Allostatic Load**

From the biobehavioral perspective, the concept of allostasis has been utilized to study the impact of chronic stress on biological aging and health. Allostasis refers to the adaptive process whereby physiological systems fluctuate and maintain stability to match environmental demands (McEwen & Seeman, 1999). Allostasis differs from the traditional homeostatic models which conceptualize health as static biological set-points; allostasis defines health as a dynamic state of responsiveness, which adapts constantly to environmental demands (Juster, McEwen, & Lupien, 2010). Aging impairs an organism’s ability to sustain efficient allostasis in response to stressors (Epel, 2009). Chronic stress can accelerate this biological aging process by changing physiological systems’ regulatory profiles such as cortisol levels, blood pressure, and cytokines (McEwen, 2003). For each bodily system, there are both short-term adaptations (allostasis) that are energy-provoking and protective against pathogens and long-term effects that can be damaging (allostatic load) (McEwen & Seeman, 1999). An index of these biomarkers conceptualized as allostatic load (AL) measures the degree of biochemical damage due to fluctuation of individuals’ stressor exposures and adaptations. A high AL index has been associated with earlier mortality (Epel, 2009).

There are four key features of the allostasis and AL model (McEwen, 2008). The concept emphasizes the integrative role of the brain for coordinating behavioral and
neuroendocrine response to stress. It also emphasizes the substantial individual differences in coping with stress, in terms of genetic inheritability and developmental and experiential trajectories. Third, the neuroendocrine responses are wired to be protective in the short term, and it is vital for neuroendocrine system to turn the stress response on and off efficiently. Finally, the price the body pays for inefficient responses to stress is reflected in AL, thus AL hosts the vicissitudes of individuals’ life that is conceptually the mediators of allostasis.

Allostasis and AL are general concepts to be applied in studying physiological responses. To know how each system of the body responds physiologically, however, requires understanding the underlying mechanisms of the mediators that have organ- and tissue-specific effect by acting via receptors. The specific mediators of allostasis include primarily adrenal steroids and catecholamines, and other hormones like DHEA, growth hormones, and the cytokines of the immune system (McEwen, 1998). Protection and damage are the contrasting effects of physiology to defend the body against daily challenges (McEwen, 2003, 2008). When a hormone/mediator is released, the action has both short-term and long-term consequences on cell functioning, which in turn is consequential on physical health. Take the metabolism for example. While adrenal steroids facilitate the replenishment of energy reserves in the short run, the overactive metabolism in the long run involves repeated hypothalamic-pituitary-adrenal (HPA) reactivity to stress, and elevated cortisol levels lead to AL in terms of insulin resistance, greater vulnerability of Type II diabetes, abdominal obesity, atherosclerosis, and hypertension (McEwen & Seeman, 1999).

_Hypothalamic-pituitary-adrenal (HPA) Axis Functioning_
The major part of the neuroendocrine systems that has implication in stress functioning is the hypothalamic-pituitary-adrenal (HPA) axis, which regulates many important bodily processes in reaction to stress, including metabolism, digestion, immune system, mood and emotions, cognition, and sexuality. The HPA axis is one potential biological mechanism for how chronic stress gets under the skin (Miller, Chen, & Zhou, 2007). Because of the central role HPA plays in reaction to stress and its sensitivity to both psychosocial and physical stress, its neuroendocrine functioning and hormone products have attracted particular research attention.

Briefly, when the brain detects a stimulus, the neurons in the paraventricular nucleus of the hypothalamus produces corticotrophin-releasing hormone (CRH). CRH gets through the hypophyseal portal circulation to the anterior pituitary gland, which responds by releasing a pulse of adrenocorticotropic hormone (ACTH), as well as arginine vasopressin (AVP), which is central to the fight-or-flight response (Dickerson & Kemeny, 2004; Piazza, Almeida, Dmitrieva, & Klein, 2010). Then ACTH gets through the peripheral circulation to the adrenal glands, which produce cortisol in a tissue layer of zona fasciculata (Sapolsky, Krey, & McEwen, 1986). The primary hormone/mediators of the HPA axis are CRH, ACTH, AVP, dehydroepiandrosterone (DHEA) and its sulfated form DHEA-S, and cortisol. DHEA(-S) is similar to cortisol, because it is probably coreleased with cortisol in response to ACTH signaling. However, DHEA(-S) is anabolic, while cortisol is a catabolic hormone (Epel, 2009). Anabolic hormones such as androgens (DHEA(-S), and testosterone) are important for stress and aging. These hormones are often associated with poor metabolic health, and they decrease with age. DHEA(-S) often functions as an antiglucocorticoid and has buffering effects on inflammation and oxidative stress. DHEA(-S) can prevent oxidative stress damage in neurons, and it can block cortisol-mediated excitatory neurotoxicity. 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. Thus the balance between cortisol and DHEA(-S) has important health implications (Epel, 2009).

As the end product of this cascade, cortisol has been the center of research because of its regulatory functions and relatively easy access to measurement. Cortisol is key in the central nervous system for learning, memory, and emotion, in the metabolic system for glucose reserve and utilization, in the immune system for regulating inflammatory responses and lymphocytes activity. Besides these prominent functions, cortisol is also important for other bodily systems (Miller et al., 2007). Cortisol activity is responsive to acute stressors. Dickerson and colleagues conducted a meta-analysis based on 208 lab studies of acute psychological stressors (Dickerson & Kemeny, 2004). They found that motivated performance tasks activated cortisol responses if they were uncontrollable or the threat was appraised as social in nature. That is, lab tasks with uncontrollability that threaten the social self were associated with the largest increase in cortisol and adrenocorticotropin hormone changes. These increases also took the longest times to recover.

In addition, cortisol is the hypothesized biological mechanism for stress to bring about mal-function and disease in the body. Similar to the acute stress responses induced in lab settings, cortisol also responds to chronic stressors, and such models have been applied to psychiatric disorders of depression, medical conditions of cancer and diabetes, and lifestyle problems such as obesity and fatigue. Chronic stressors can both increase or decrease cortisol output. Many of these models articulate that stress triggers disease by increasing cortisol output (hypercortisolism), exposing tissues to its elevated concentrations. However, cortisol deficiency has also been related to disease pathogenesis such as posttraumatic stress disorder, rheumatoid
arthritis, and chronic fatigue. Thus, stress-induced increases or decreases in cortisol output (hypocortisolism) are both detrimental in a similar way.

The ideas presented here will be explored in the three studies that follow. Specifically, this dissertation tries to clarify the physiological implications of caregiving among older dementia caregivers in various daily contexts. A special focus will be exploring whether adult day service use among caregivers truly has some health benefits besides its known values for caregiver well-being.
CHAPTER 2. STUDY 1

Modeling Daily Cortisol Rhythms of Family Caregivers of Individuals with Dementia:

Daily Stressors and Adult Day Services (ADS) Use

2.1 Background and Literature Review

Prior studies of caregiving have shown that the chronic stress of assisting loved ones with disabilities may place caregivers at heightened risk for compromised health and well-being (i.e., Zarit, Kim, Femia, Almeida, & Klein, 2014; Pinquart & Sörensen, 2003b). The stress of caregiving manifests itself physiologically, with some caregivers showing biological dysregulation, including for daytime cortisol responses (Klein et al., 2014). Cortisol has many regulatory functions; it plays an important role in the central nervous system for learning, memory, and emotion, in the metabolic system for glucose reserve and utilization, in the immune system for regulating inflammatory responses and lymphocytes activity (Miller, Chen, & Zhou, 2007). Besides these prominent functions, cortisol is also important for other bodily organs such as the liver and kidney (Weiner, 1992). Studies have shown that cortisol is responsive to acute as well as chronic stressors (Miller, Chen, & Zhou, 2007). These cortisol responses may provide a link between daily experiences and health. In other words, cortisol is considered one of the hypothesized biological mechanisms by which stress brings about malfunction and disease in the body (Almeida, Piazza, Stawski, & Klein, 2011). Evidence for the cortisol-health link has been found for psychiatric disorders of depression, medical conditions of cancer and diabetes, and lifestyle problems such as obesity and fatigue (Abercrombie et al., 2004; Abraham, Rubino, Sinaii, Ramsey, & Nieman, 2013; Bremmer et al., 2007; Bruehl et al., 2007; Powell, Liossi, Moss-Morris, & Schlotz, 2013).
Given these links of cortisol to stressful situations and health, the present study examines how daily caregiving is associated with diurnal rhythms of cortisol. Using daily diaries, the current study focused on aging family caregivers of individuals with dementia (IWDs) who utilized adult day services (ADS) at varying amount of days during the week. Caregivers’ cortisol samples were collected five times a day for eight consecutive days, along with daily interviews on their daily stressor experiences. The study expands prior research in three ways. First, it explores and describes the best-fitting typical diurnal cortisol curve based on different statistical models. Second, the impact of an intervention, ADS use, which lowers care stressor exposure (Zarit et al., 2011), is tested using the best-fitting model by comparing caregivers on days they use ADS and days they do not. Third, ADS effects on cortisol are re-evaluated in the context of daily stressors.

**Measures of diurnal cortisol rhythm**

One common parameter of diurnal cortisol regulation is the level change as a function of time elapsed, or cortisol slopes. Compared with the composite measure of cortisol regulation such as area under the curve, cortisol diurnal slopes afford a close-up examination of cortisol level changes across specific time frames throughout the day and its diurnal profiles. The slopes can then be associated with predictors to examine their distinctive effects on cortisol diurnal level change. Some commonly studied slopes include the cortisol awakening response (CAR) slope and diurnal decline slopes (e.g., Stalder et al., 2015). Salivary cortisol typically has a rapid rise upon awakening, the CAR, which has been utilized as an index of hypothalamic–pituitary–adrenal (HPA) activity. In healthy adults, salivary cortisol increases by between 50 to 160% in the first 30 - 45 minutes after awakening. Although perceived chronic stress and anticipated acute stressors were associated with CAR and cortisol declining slopes (Clow, Thorn, Evans, &
Hucklebridge, 2004; Stawski, Cichy, Piazza, & Almeida, 2013), the nature of association varied with some studies showing cortisol elevation and others showing lower cortisol levels and attenuated slopes (Chida & Steptoe, 2009). Flattened cortisol slopes were typically expected in samples that were experiencing chronic stress and older (e.g., Strahler, Berndt, Kirschbaum, & Rohleder, 2010).

CAR varies substantially both within and across individuals. Factors such as waking time, sleep duration and quality, caffeine consumption, smoking, and steroid use can influence CAR variation (Hellhammer et al., 2007). Further, cortisol levels are sensitive to sampling time (Clow et al., 2004). Poor participant adherence to collection protocols has also been associated with attenuated CAR and diurnal slopes (Adam & Kumari, 2009). To better accommodate both within- and between-person variations in sampling time and factors associated with differential cortisol diurnal trajectories, Ranjit and colleagues (2005) suggested using a piecewise linear regression model with random effects, which is essentially a zero-degree spline-based model, also known as the linear spline model. Specifically, the diurnal cortisol levels were modeled using multiple joined pieces of linear components as a function of time elapsed since wake-up. The joining locations of the linear components are defined as knots (Wold, 1974).

Ranjit, Young, Raghunathan, & Kaplan (2005) suggested some advantages of such modeling approaches, which include cortisol samples not needing to be evenly distributed over the course of the day, and accommodating participants’ unequal number of samples during the study period. A more intensive daily cortisol sampling scheme can usually generate smoother curves, which may offer better model fit. Such growth curve approaches utilize the spline function, defined as the piecewise polynomial; the polynomials join in the knots, generating a high degree of smoothness (Wold, 1974). Additionally, these models can best accommodate
variation in the sampling time, which is typical in daily cortisol studies using a diary design. This model and its variations have been applied to population-based samples (Karlamangla et al., 2013; Ranjit, Young, & Kaplan, 2005), but they have not been tested in a dementia caregiver sample. Unlike the general population, family caregivers of IWDs are considered under chronic stress, and they experience relatively high levels of daily stressors. Some behavior problems of IWDs, for example, can be emotionally and physiologically provoking on a day-to-day basis. Thus, the specific stress context of dementia caregivers versus the general population may have some implications on what would be the most appropriate model for diurnal cortisol regulation among caregivers.

There can be more than one growth curve model for the typical diurnal cortisol slopes (Karlamangla et al., 2013). Using linear spline growth curves, the nuances in the declining slopes during different time windows across the day can be modeled with fixed inflection time points (Ranjit, Young, Raghunathan, et al., 2005); using linear-quadratic and linear-cubic growth curves, smoother declining slopes can be modeled (Karlamangla et al., 2013). It is unclear, however, which piecewise growth curve model can best capture dementia caregivers’ cortisol diurnal shape and account for its natural variability in the context of specific daily experiences of caregiving. The current study explores the best model of diurnal cortisol slopes using three different piecewise growth curves, based on five daily measures from a dementia caregiver sample. Describing the best-fitting typical diurnal curve serves as the first aim for the study.

**The adult day services hypothesis**

Caregivers’ use of ADS has been shown to affect variation in their daily stressor exposures (e.g., Zarit, Kim, et al., 2011; 2014). As respite, ADS is intended to relieve some of
the care-related stressor exposures. Use of ADS potentially renders some days to be high-stress whereas others low-stress. On day-care days, caregivers have lower exposure to care-related stressors, but slightly higher exposure to non-care stressors (Zarit, Kim, et al., 2014). Prior studies of ADS have shown health benefits at both within- and between-person levels for family caregivers of IWDs. Caregivers have lower depressive symptoms and less fluctuation in negative affect on ADS days than non-ADS days; caregivers who utilized ADS at a greater extent also have less physical health decline over 12 months (i.e., Liu, Kim, & Zarit, 2015; Liu, Kim, Almeida, & Zarit, 2015; Zarit, Kim, et al., 2014). More recent studies have shown some physiological benefits of ADS use on caregivers’ stress hormones such as cortisol (i.e., Klein et al., 2014). These studies have typically relied on summary measures of cortisol outcome such as the daily total output calculated as the area under the curve and CAR calculated as the cortisol level differences between the two waking samples. There are few studies that examined dementia caregivers’ diurnal cortisol slopes using piecewise growth curves in the context of an intervention, the ADS use, and daily stressors. It is unclear whether this approach might pinpoint more effectively if there is any within- or between-person associations with ADS use on caregivers’ diurnal cortisol slopes. The second aim of the current study is to seek answers to this question.

**Daily stressors and diurnal cortisol rhythms**

Daily stressors are common and often recurring challenges people encounter every day in their social settings and naturalistic environments. Depending on their frequency, type, duration, and objective severity, daily stressors can be acute and chronic (Almeida, 2005). Acute stressors are more “unexpected small occurrences” often with a beginning and an end such as family arguments, interpersonal stressors, and a computer malfunction. Chronic stressors, in contrast,
are more persistent, irritating, and resistant to change. Such events include the daily stressors frequently encountered while providing care to dementia patients.

Prior research has focused on both acute and chronic stressors and cortisol diurnal rhythms using the piecewise growth curve approach. Following this line of research, Stawski and colleagues (2013) used a piecewise linear-quadratic model and found that people who experienced acute daily stressors more frequently exhibited a steeper diurnal cortisol slope that decelerated more rapidly. Using a quadratic growth curve model, Savla and colleagues (2013) examined daily stressors in spouses of persons with mild cognitive impairment. They found that on days caregivers reported any mood disturbances of their spouse, they showed a flatter cortisol rhythm with elevated daily cortisol output. Using a four-part piecewise linear regression model, Ranjit and colleagues (2005) found that women with more marital hardship had flattened cortisol rhythms, with lower rise upon awakening and a less steep decline throughout the day than women with low levels of hardship. Using three alternative piecewise growth curves, Karlamangla and colleagues (2013) found that daily cortisol rhythm was flatter and more blunted in individuals with less privileged social status characterized by lower education and ethnic minority background.

Dementia caregivers are generally considered to be under chronic stress. Additionally, they also tend to experience relatively high levels of daily stressors compared with non-caregivers (Mausbach et al., 2012). Depending on the care situation, caregivers may encounter a varying number of daily stressors that are care-related, additional stressors not related to providing care as well as some positive events (Zarit, Kim, et al., 2014). Care-related stressors are usually operationalized as the behavior problems of IWDs; care-related stressors tend to evoke different degrees of subjective reactivity depending on the nature and severity of the
stressors (Aneshensel, Pearlin, Mullan, Zarit, & Whitlatch, 1995). Prior studies have primarily examined the associations between daily stressors and summary measures of cortisol daily total output and CAR (Klein et al., 2014); few studies have examined within-person patterns of diurnal cortisol slopes in relation to these different daily caregiving stressors and positive events. The third aim of the current study is to evaluate the effects of ADS use on the entire cortisol diurnal curves in the context of distinctive types of stressors, based on the best-fitting model at both within- and between-person levels. Daily variables shown to covary with cortisol outcomes in prior studies such as daily wakeup time, sleep duration and quality are considered as covariates of cortisol diurnal slopes in the current study (e.g., Stawski et al., 2013).

The current study has the following hypotheses based on the best-fitting model of diurnal cortisol rhythms.

**Hypothesis 1:** ADS use will be associated with cortisol regulation at both within- and between-person levels. Specifically, daily ADS use (i.e., at the within-person level) as well as total number of ADS days per week (i.e., at the between-person level) are expected to associate, respectively, with a steeper CAR slope and steeper declining slopes across the day.

**Hypothesis 2:** The associations between ADS use and diurnal cortisol slopes are expected to remain significant after controlling for daily stressor exposures. Specifically, a full model will be run with ADS use and variables of daily stressor exposures as predictors. The purpose of this full model is to examine if ADS use is still significantly associated with diurnal cortisol slopes in the daily stress context.

### 2.2 Methods

**Participants**
Participants were 176 family caregivers from the *Daily Stress and Health* (DaSH) study (Zarit et al., 2014). To be eligible, caregivers had to be: a) providing primary care to an IWD that lived in the same household, and b) using ADS programs at least two days a week. In addition, the person they were caring for had to have a diagnosis of a dementing illness made by a physician.

As part of the study, participants were asked to complete 8 days of daily interviews, which were gathered each evening by telephone, and to provide 5 saliva samples each day. From the sample of 176 caregivers, 11 participants (6.3%) were excluded from the analysis. Three had mixed up or missed salivettes (1.7%) and two (1.1%) were sisters who shared care responsibilities equally. An additional six caregivers (3.4%) were excluded who only provided a homogeneous set of interviews (i.e., all ADS or all non-ADS days). Table 1 presents demographic characteristics of caregivers and the IWD they were caring for.

In total, the working sample consisted of 165 caregivers, who provided 6,234 cortisol samples (94.5% compliance) on 1,299 valid diary days (98.4% compliance) that were available for analysis. Samples with missing values or collection times \(n = 261\) were excluded. Of the 6,234 useable samples, 6,132 were valid (98.4%). A cortisol sample was not valid if: 1) the participant was awake for less than 12hr or greater than 20hr \(n = 14\), or 2) there was a greater than 10nmol rise between the second (30-min after getting out of bed) and third sample (before lunch) \(n = 11\), or 3) the recorded collection time between the first (upon wakeup) and second sample is either less than 15min or greater than 60min \(n = 99\). Among these 6,132 valid cortisol samples, 3,189 (52%) in total were collected on ADS days \(mean = 4.16, SD = 1.44\), and 2,943 were collected on days \(mean = 3.78, SD = 1.43\) when IWDs were at home with their family caregivers.
Procedures

ADS programs were identified through regional and state associations. Programs that agreed to participate were provided with detailed information about the study, recruitment brochures, and announcements that could be included in the newsletters. Fifty-seven ADS programs expressed interest in study participation. Caregivers were phoned by the research coordinator, given additional information about the study, and screened for eligibility. Subsequently, an initial face-to-face interview was conducted at the caregiver’s home, during which they signed consent forms and completed a set of questionnaires. After the initial meeting and baseline assessment, caregivers participated in daily interviews for 8 consecutive days via evening phone calls (conducted by the staff at the Penn State Survey Research Center); they also provided saliva samples five times each day. Caregivers received $100 for completing the daily and biomarker study protocol.

To collect saliva samples, participants were instructed to: 1) take saliva samples at specified times during the day by chewing on a cotton swab for 2 minutes, 2) record their saliva collection times, 3) avoid taking samples within 30 minutes of eating, drinking, brushing teeth, using tobacco or caffeinated products, and 4) refrigerate saliva samples until the end of the 8 days. Additionally, participants recorded medications taken over the past 48 hours, tobacco smoking status, and, for females, information on the menstrual cycles. Instructions for saliva collection were also reviewed during the first phone interview. At the end of the saliva collection period, salivettes were couriered to the lab at the Pennsylvania State University where they were frozen at -80 degrees C until assayed.

Measures
Saliva samples. On each of the diary study days, participants provided five saliva samples: upon wakeup, 30-min after getting out of bed, before lunch, late afternoon, and before bed. They recorded the exact sample collection time, which was also confirmed during the evening interview. Salivary cortisol levels were assayed at The Pennsylvania State University’s General Clinical Research Center using commercially available enzyme immunoassay kits (EIA; DSL, Webster, TX). The sample test volume was 25 ul. The assay had a lower limit of sensitivity of 0.03 μg/dl, with an average inter- and intra-assay covariance of less than 7% and 4%, respectively. Samples from each participant were tested in duplicate in a single assay batch. Duplicate test values that varied by more than 5% were tested repeatedly. Values used in data analyses are the averages of duplicate tests. Cortisol measurement units were converted to nmol/l (μg/dl × 27.6). Raw cortisol distribution was examined to see if log transformation is necessary for the analysis.

ADS use. In each daily diary interview the caregivers indicated whether they had made use of ADS that day. From these reports, both time-varying and time-invariant variables were derived. Daily ADS use (time-varying and within-person) was a binary variable indicating use (= 1) or nonuse (= 0) that day. Time-invariant ADS use (between-person) was computed as the sum of total ADS days across the daily interview period.

Daily stressors. Two types of daily stressors were assessed: care-related stressors and non-care stressors. Care-related stressors reflect the IWD’s daily behavior problems and were measured using the Daily Record of Behavior (DRB). The DRB, designed specifically for use in daily diaries, assesses the frequency with which 19 behaviors occurred over a 24-hour time frame (α = .78, see Femia, Zarit, Stephens, & Greene, 2007 for detailed psychometric properties). To assist caregivers in reporting behavior problems, the day is broken up into four time-blocks.
that correspond to the modal periods during which caregivers use ADS: a) waking to 9:00 a.m., b) 9:00 a.m. to 4:00 p.m. (typical ADS attendance hours), c) 4:00 p.m. to bedtime, and d) overnight. For each period of the day, caregivers were asked whether each behavior had occurred (yes/no). From these reports, both time-varying and time-invariant variables were derived. The time-varying care-related stressors were the sum of total behavior occurrences that were reported that day, including the overnight period of the previous day; the time-invariant care-related stressors were the average level of daily behavior occurrences reported across the interview period.

Non-care stressors were measured using the Daily Inventory of Stressful Events (DISE; Almeida, Wethington, & Kessler, 2002). Each evening, caregivers reported on the occurrence (yes/no) of eight events over the previous 24-hour period ($\alpha = .59$): arguments with other people, whether they avoided an argument with someone, incidents concerning their friends or family, health-related issues, money or finance-related issues, work-related issues, and other stressful issues or incidents. In order to separate care-related from non-care stressors, caregivers were specifically instructed to report events they found stressful other than those encountered when assisting their relative. Both time-varying and time-invariant variables were derived based on the daily reports. The time-varying non-care stressors were the sum of stressors reported across all eight categories on each of the diary interview days; the time-invariant non-care stressors were the average level of daily stressors reported across the interview period.

**Daily positive events.** Using five items drawn from the DISE (Sin, Graham, & Almeida, 2014), caregivers reported occurrences of positive experiences during the past 24 hours ($\alpha = .63$): sharing a laugh with someone, having an experience at home, with a close friend or relative, or at work that others would consider positive, and any other positive experience. Both time-varying and time-invariant variables based on the daily reports were derived. The time-varying variable
was the sum of positive events reported based on all five categories on each of the diary interview days; the time-invariant variable was the average level of daily positive events across the interview period.

**Covariates.** Additional variables that are often associated with caregivers’ cortisol levels were considered as covariates. Caregivers’ chronological age, gender (1 = *female* and 0 = *male*), duration of care provision (*months*), the IWD’s ADL dependency (mean of 13 items; coded on a 4-point scale; 1 = *does not need help* to 4 = *cannot do without help*; higher scores indicated greater dependency; α = .83), caregiver sleep quality assessed each day as the response to the item: “Rate the quality of your sleep last night” (5-point scale; 1 = *poor* to 5 = *excellent*), caregiver self-reported wake-up time, and sleep duration calculated as the time difference between self-reported wake-up and bedtime. Caregivers’ daily sleep quality, wake-up time and sleep duration were used as time-varying covariates and caregivers’ average sleep quality, wake-up time, and sleep duration across days were used as time-invariant covariates.

**Analytical strategy**

Prior studies have shown that cortisol level is driven primarily by time elapsed since wakeup and less by the clock time. This study, therefore, modeled daily cortisol trajectories as a function of time elapsed since wakeup. Although caregivers were instructed to collect the second saliva sample 30 minutes after getting out of bed, significant variation in actual sample collection time was expected, with the second sample collected between 15 minutes and 45 minutes after wakeup in 94.1% of all valid cortisol samples. Similarly, greater variation was expected in the collection time for the other saliva samples throughout the day due to vastly varying daily routines and experiences. Thus it was possible to model caregivers’ cortisol levels
at different sampling times and to examine the factors associated with different trajectories of the typical daytime cortisol trajectory.

Based on prior studies on daily cortisol (Karlamangla et al., 2013), a typical trajectory across the day can be represented by a linearly increasing segment during the 30 minutes of awakening, and a gradual decline throughout the day, with a slight uptick slope on some days with a very long sampling duration. This study adopted the piecewise growth curve approach and compared model fit among three fitted growth curves of diurnal cortisol using a) a four-part piecewise linear spline model, b) a linear-quadratic spline model, and c) a linear-cubic spline model. The linear spline model had four linear components, joining in the fixed knots at 0.5hr, 6hr, and 10.5hr after wakeup, which allowed the timing of the cortisol peak to vary across individuals. The linear-quadratic and linear-cubic spline models had a linear and a higher order polynomial component (i.e., a second order for quadratic function versus a third order for cubic function), which joined in the only fixed knot at 0.5hr after wakeup. As there can be more than one way to determine the location of knots, these fixed knots (i.e., inflection time points) were determined based on the observed average cortisol sampling time as suggested by Ranjit, Young, Raghunathan, & Kaplan (2005). A 3-level unconditional model was used to model the cortisol diurnal curves because there were significant variance components at both the across-day and between-person levels. Such models can account for within-day and across-day correlations in cortisol levels. Time was the independent variable for within-day cortisol equation. Covariates at the across-day and between-person levels were added to the corresponding levels of equations. Then these three unconditional multilevel models were compared for the best model fit for the current caregiver sample. Finally, to test hypotheses on ADS use and the daily context of stressors, the best-fitting unconditional model was expanded to include key predictors and
covariates in the appropriate level of equations. For all three models, the fixed effects of $\beta$s are of primary interest.

For the four-part linear spline model, the growth curve parameters were the following (the fixed knots where the linear components join in were suggested by examining the average cortisol sampling time): intercept, CAR slope, the first linear decline slope from 30min after waking to before lunch (AD1), the second linear decline slope from before lunch to late afternoon (AD2), and the third linear decline slope from late afternoon to before bed (AD3). To test hypotheses, the full 3-level linear spline model was specified as:

**Level 1 (Within-day level):**

\[
\text{Cortisol}_{si} = \pi_{0di} + \pi_{1di} (\text{CAR}_{si}) + \pi_{2di} (\text{AD1}_{si}) + \pi_{3di} (\text{AD2}_{si}) + \pi_{4di} (\text{AD3}_{si}) + \epsilon_{si}
\]

**Level 2 (Across-day level):**

\[
\begin{align*}
\pi_{0di} &= \beta_{00i} + \beta_{01i} (\text{ADS}_{di}) + \beta_{02i} (\text{Daily non-care stressors}_{di}) + \beta_{03i} (\text{Daily care-related stressors}_{di}) + \beta_{04i} (\text{Daily positive events}_{si}) + \beta_{05i} (\text{Daily sleep quality}_{di}) + \beta_{06i} (\text{Daily sleep duration}_{di}) + \beta_{07i} (\text{Daily wake-up time}_{di}) + \nu_{0di} \\
\pi_{1di} &= \beta_{10i} + \beta_{11i} (\text{ADS}_{di}) + \nu_{1di} \\
\pi_{2di} &= \beta_{20i} + \beta_{21i} (\text{ADS}_{di}) + \nu_{2di} \\
\pi_{3di} &= \beta_{30i} + \beta_{31i} (\text{ADS}_{di}) + \nu_{3di} \\
\pi_{4di} &= \beta_{40i} + \beta_{41i} (\text{ADS}_{di}) + \nu_{4di}
\end{align*}
\]

**Level 3 (Between-person level):**

\[
\begin{align*}
\beta_{00i} &= \gamma_{000} + \gamma_{001} (\text{Sum of ADS days}_i) + \gamma_{002} (\text{Average non-care stressors}_i) + \gamma_{003} (\text{Average care-related stressors}_i) + \gamma_{004} (\text{Average positive events}_i) + \gamma_{005} (\text{Average sleep quality}_i) + \gamma_{006} (\text{Average sleep duration}_i) + \gamma_{007} (\text{Average wake-up time}_i) + \gamma_{008} (\text{Gender}_i) + \gamma_{009} (\text{Duration of care}_i) + \gamma_{0010} (\text{IWD’s ADL dependency}_i) + \gamma_{0011} (\text{Age}_i) + u_{00i} \\
\beta_{01i} &= \gamma_{010} \\
\vdots \\
\beta_{07i} &= \gamma_{070} \\
\beta_{10i} &= \gamma_{100} + \gamma_{101} (\text{Sum of ADS days}_i) + \gamma_{102} (\text{Average non-care stressors}_i) + \gamma_{103} (\text{Average care-related stressors}_i) + \gamma_{104} (\text{Average positive events}_i) + \gamma_{105} (\text{Average sleep quality}_i) + \gamma_{106} (\text{Average sleep duration}_i) + \gamma_{107} (\text{Average wake-up time}_i) + \gamma_{108} (\text{Gender}_i) + \gamma_{109} (\text{Duration of care}_i) + \gamma_{1010} (\text{IWD’s ADL dependency}_i) + \gamma_{1011} (\text{Age}_i) + u_{10i} \\
\beta_{11i} &= \gamma_{110}
\end{align*}
\]
\[ \beta_{20i} = \gamma_{200} + \gamma_{201} \text{(Sum of ADS days}_i) + \gamma_{202} \text{(Average non-care stressors}_i) + \gamma_{203} \text{(Average care-related stressors}_i) + \gamma_{204} \text{(Average positive events}_i) + \gamma_{205} \text{(Average sleep quality}_i) + \gamma_{206} \text{(Average sleep duration}_i) + \gamma_{207} \text{(Average wake-up time}_i) + \gamma_{208} \text{(Gender}_i) + \gamma_{209} \text{(Duration of care}_i) + \gamma_{2010} \text{(IWD’s ADL dependency}_i) + \gamma_{2011} \text{(Age}_i) + u_{20i} \]

\[ \beta_{31i} = \gamma_{310} \]

\[ \beta_{30i} = \gamma_{300} + \gamma_{301} \text{(Sum of ADS days}_i) + \gamma_{302} \text{(Average non-care stressors}_i) + \gamma_{303} \text{(Average care-related stressors}_i) + \gamma_{304} \text{(Average positive events}_i) + \gamma_{305} \text{(Average sleep quality}_i) + \gamma_{306} \text{(Average sleep duration}_i) + \gamma_{307} \text{(Average wake-up time}_i) + \gamma_{308} \text{(Gender}_i) + \gamma_{309} \text{(Duration of care}_i) + \gamma_{3010} \text{(IWD’s ADL dependency}_i) + \gamma_{3011} \text{(Age}_i) + u_{30i} \]

\[ \beta_{40i} = \gamma_{400} + \gamma_{401} \text{(Sum of ADS days}_i) + \gamma_{402} \text{(Average non-care stressors}_i) + \gamma_{403} \text{(Average care-related stressors}_i) + \gamma_{404} \text{(Average positive events}_i) + \gamma_{405} \text{(Average sleep quality}_i) + \gamma_{406} \text{(Average sleep duration}_i) + \gamma_{407} \text{(Average wake-up time}_i) + \gamma_{408} \text{(Gender}_i) + \gamma_{409} \text{(Duration of care}_i) + \gamma_{4010} \text{(IWD’s ADL dependency}_i) + \gamma_{4011} \text{(Age}_i) + u_{40i} \]

\[ \beta_{41i} = \gamma_{410} \]

where the intercept was the cortisol level at wakeup and each of the linear slope represented cortisol level changes as a function of time elapsed since wakeup. The control variables were entered as main effects only. To test for hypotheses on ADS use and the daily context of stressors on the slopes at both within- and between-person levels, time-varying and time-invariant predictors were entered into the day- and person-level equations to interact with each of the four cortisol diurnal slopes.

For the linear-quadratic spline model, the growth curve parameters were the following: intercept, CAR slope, linear decline, and quadratic decline. The intercept was the cortisol level at wakeup. The linear decline slope modeled the declining rate that began 30 minutes after waking, and the quadratic decline slope modeled any deceleration rate that began 30 minutes after waking. The unconditional 3-level linear-quadratic spline model was specified as:

**Level 1 (sample level):**

\[ \text{Cortisol}_{edi} = \pi_{0di} + \pi_{1di} \text{(CAR}_{edi}) + \pi_{2di} \text{(ADL}_{edi}) + \pi_{3di} \text{(ADL}^2_{edi}) + \epsilon_{edi} \]
Level 2 *(day level)*:
\[
\begin{align*}
\pi_{0di} &= \beta_{00i} + v_{0di} \\
\pi_{1di} &= \beta_{10i} + v_{1di} \\
\pi_{2di} &= \beta_{20i} + v_{2di} \\
\pi_{3di} &= \beta_{30i} + v_{3di}
\end{align*}
\]

Level 3 *(person level)*:
\[
\begin{align*}
\beta_{00i} &= \gamma_{000} + u_{00i} \\
\beta_{01i} &= \gamma_{010} \\
\beta_{02i} &= \gamma_{020} \\
\beta_{03i} &= \gamma_{030} \\
\beta_{04i} &= \gamma_{040} \\
\beta_{10i} &= \gamma_{100} + u_{10i} \\
\beta_{11i} &= \gamma_{110} \\
\beta_{12i} &= \gamma_{120} \\
\beta_{13i} &= \gamma_{130} \\
\beta_{14i} &= \gamma_{140} \\
\beta_{20i} &= \gamma_{200} + u_{20i} \\
\beta_{21i} &= \gamma_{210} \\
\beta_{22i} &= \gamma_{220} \\
\beta_{23i} &= \gamma_{230} \\
\beta_{24i} &= \gamma_{240} \\
\beta_{30i} &= \gamma_{300} + u_{30i} \\
\beta_{31i} &= \gamma_{310} \\
\beta_{32i} &= \gamma_{320} \\
\beta_{33i} &= \gamma_{330} \\
\beta_{34i} &= \gamma_{340}
\end{align*}
\]

For the linear-cubic spline model, the growth curve parameters were the following: intercept, CAR slope, linear decline, quadratic decline, and cubic decline. The intercept was the cortisol level at wakeup. CAR slope was the cortisol awakening slope per hour, and the linear, quadratic, and cubic slopes were the parameters of the cubic recovery curves that began 30 minutes after wakeup. The unconditional 3-level linear-cubic spline model was specified as:

Level 1 *(sample level)*:
\[
\text{Cortisol}_{sdi} = \pi_{0di} + \pi_{1di} (\text{CAR}_{sdi}) + \pi_{2di} (\text{AD}_{sdi}) + \pi_{3di} (\text{AD}^2_{sdi}) + \pi_{4di} (\text{AD}^3_{sdi}) + \varepsilon_{sdi}
\]

Level 2 *(day level)*:
\[
\pi_{0di} = \beta_{00i} + v_{0di} \\
\pi_{1di} = \beta_{10i} + v_{1di} \\
\pi_{2di} = \beta_{20i} + v_{2di} \\
\pi_{3di} = \beta_{30i} + v_{3di} \\
\pi_{4di} = \beta_{40i} + v_{4di}
\]

Level 3 (person level):
\[
\beta_{00i} = \gamma_{000} + u_{00i} \\
\beta_{01i} = \gamma_{010} \\
\beta_{02i} = \gamma_{020} \\
\beta_{03i} = \gamma_{030} \\
\beta_{04i} = \gamma_{040} \\
\beta_{10i} = \gamma_{100} + u_{10i} \\
\beta_{11i} = \gamma_{110} \\
\beta_{12i} = \gamma_{120} \\
\beta_{13i} = \gamma_{130} \\
\beta_{14i} = \gamma_{140} \\
\beta_{20i} = \gamma_{200} + u_{20i} \\
\beta_{21i} = \gamma_{210} \\
\beta_{22i} = \gamma_{220} \\
\beta_{23i} = \gamma_{230} \\
\beta_{24i} = \gamma_{240} \\
\beta_{30i} = \gamma_{300} + u_{30i} \\
\beta_{31i} = \gamma_{310} \\
\beta_{32i} = \gamma_{320} \\
\beta_{33i} = \gamma_{330} \\
\beta_{34i} = \gamma_{340} \\
\beta_{40i} = \gamma_{400} + u_{40i} \\
\beta_{41i} = \gamma_{410} \\
\beta_{42i} = \gamma_{420} \\
\beta_{43i} = \gamma_{430} \\
\beta_{44i} = \gamma_{440}
\]

2.3 Results

The mean and standard deviation on salivary cortisol sampling times and levels are presented in Table 1. Substantial variation in cortisol sampling time and levels was observed within caregivers across days and between caregivers. To evaluate associations between cortisol levels, daily experiences, and caregiving characteristics, preliminary models were run first using
cortisol levels at each sampling occasion as outcomes. Parameter estimates of these preliminary models are presented in Table 2. In general, shorter sleep durations tended to be associated with higher cortisol levels across all sampling occasions. Additionally, higher cortisol levels upon awakening ($\beta = 0.07, p = 0.04$) and in the late afternoon ($\beta = 0.04, p = 0.04$) were associated with older caregiver age. Higher cortisol levels at 30 minutes after waking was associated with daily ADS use ($\beta = 1.21, p = 0.002$) and more positive daily experiences ($\beta = 0.96, p = 0.02$). Higher before-lunch cortisol levels were associated with shorter previous night’s sleep duration ($\beta = -0.25, p = 0.02$), later daily wake-up time ($\beta = 0.34, p = 0.008$), and being male ($\beta = -1.03, p = 0.03$). Higher late-afternoon cortisol levels were associated with a poorer previous night’s sleep ($\beta = -0.41, p = 0.0009$), older age ($\beta = 0.04, p = 0.04$) and IWD’s ADL dependency ($\beta = 0.98, p = 0.03$). Higher bedtime cortisol levels were associated with more daily non-care stressors ($\beta = 0.30, p = 0.03$) and early wake-up time at the between-person levels ($\beta = -0.50, p = 0.04$).

To answer the research question of best-fitting model on diurnal cortisol rhythms among alternative piecewise growth curves, three unconditional models were run. Parameter estimates and overall model fit indices are presented in Table 3. Diurnal cortisol curves based on these three unconditional models are presented in Figure 1. For each of the alternative models, all cortisol diurnal slopes were significant. However, the four-part linear spline model had the lowest BIC (Table 3), suggesting best model fit for this dementia caregiver sample. It was therefore chosen as the base model for all ensuing analyses.

Based on the unconditional linear spline model, the sample average level of waking cortisol was 9.18 nmol/l, and CAR was 6.32 nmol/l per hour. Cortisol declined initially at 1.83 nmol/l per hour from the second to the third sampling occasion (i.e., from 30-min post awakening to before lunch), and the rate of decline decelerated at 0.25 nmol/l per hour from
before lunch to late afternoon. There was a slight uptick in cortisol levels between late afternoon and bed time at 0.07 nmol/l per hour.

Next, to test the hypothesis on ADS use and associations with diurnal cortisol slopes, two models were run with ADS use as the covariate at the within- (i.e., the daily ADS effect, Model 1) and between-person (i.e., the total ADS days used effect, Model 2) levels. Parameter estimates are presented in Table 4. Model 1 showed that the daily ADS effect was primarily in the morning. Specifically, daily ADS use was significantly associated with a more prominent CAR ($\beta = 3.26, p < 0.001$), and a steeper decline starting from 30 minutes after waking and leading to before lunch ($\beta = -0.22, p = 0.001$). On non-ADS days, however, caregivers tended to have a flatter cortisol diurnal pattern (Figure 2). Daily ADS use did not have any effect on the other two declining slopes starting from before lunch and thereafter. Model 2 showed that total ADS days across the 8-day period also had some effect on the cortisol slope between late afternoon and before bed. Specifically, more ADS days were associated with a slight but significant cortisol uptick later in the day.

To test the hypothesis on ADS use and associations with diurnal cortisol slopes in the context of daily stressor exposures, a full model as specified earlier was run with ADS effects controlling for daily experiences and caregiving characteristics such as caregiver age, gender, and duration of care (Model 3). All significant ADS effects on diurnal cortisol slopes remained. However, none of the daily stressor and positive experience interactions with cortisol slopes was significant at either the within- or between-person level. All non-significant interactions were trimmed from the final model. Parameter estimates are presented for Model 3 in Table 4.

2.4 Discussion
This study is among the first to examine dementia caregivers’ salivary cortisol diurnal rhythms in relation to an intervention, in the context of daily experiences. Prior studies using the same data set found that ADS use may have some physiological benefits with better cortisol regulation (Klein et al., 2014). Also, daily stressor exposures were found to be predictive of emotional responses to stressors, such as depression and anger, whereas ADS use, in turn, may alleviate some of these emotional responses (Zarit et al., 2014). The current study compliments this work by demonstrating at a daily level that stressor exposures among dementia caregivers are associated with increased cortisol levels at certain times of the day (i.e., before bed). Daily ADS use, was associated with a more robust CAR, which could have some physiological benefits for chronically stressed caregivers.

The study had a number of notable contributions to the literature. First, it explored three alternative spline models to see which had the best fit to the naturally occurring cortisol. Although the linear-quadratic spline and linear-cubic spline models produced smoother declining curves, the linear spline model was the best representation of the naturally occurring cortisol pattern among dementia caregivers given the data. The sample of dementia caregivers in this study was different from a general population sample in two ways. Family caregivers were under chronic stress (Aneshensel et al., 1995); meanwhile, they also tended to experience high levels of daily stressors such as behavior problems of IWDs as well as other non-care stressors (Zarit et al., 2014). Prior studies have typically utilized some form of quadratic functions to model cortisol diurnal trajectories (i.e., Savla et al., 2013; Stawski et al., 2013). Ranjit and colleagues (2005), however, recommended the piecewise linear spline as an effective way to model naturally occurring cortisol profile. Further, Karlamangla and colleagues (2013) found the piecewise linear spline model fit better than other alternative piecewise growth curve models
for a nationally representative sample. Thus, the daily stress context of the specific sample may have played a key role in determining what would be the best cortisol model.

Second, the associations between ADS use and cortisol in the context of daily experiences were complex and differed depending on whether the cortisol outcomes were the levels or diurnal slopes, and whether the associations were between-person or within-person over time. ADS use manipulated caregivers’ daily exposures to primary stressors of caregiving, the behavior problems of IWDs. On some diary days, caregivers used ADS; on the others, they actively provided care for the IWD. The finding that, at the within-person level, ADS use was significantly associated with higher levels of cortisol 30 minutes after wake-up and a more prominent CAR were consistent with prior studies (Chida & Steptoe, 2009). While in acute stress situations, increases in CAR may be considered problematic, people experiencing chronic stress including many caregivers in this sample had very low CAR, which indicates burnout. This is what was found in the current study. Furthermore, the current findings suggest the physiological benefits of ADS use. Specifically, ADS can help restore a healthier CAR and a more prominent declining cortisol profile. ADS effect remained significant even after considering the daily stressor experiences. Beyond the diminished stressor exposures associated with ADS use, there may be other positive effects. The time away from caregiving may be spent on more predictable and pleasant activities, which in turn may be reflected in more normal cortisol levels among dementia caregivers (Klein et al., 2014; Leggett, Liu, Klein, & Zarit, 2015). Given that caregivers showed changes in early morning cortisol responses (CAR) prior to their relative leaving for ADS, there may also be benefits associated with anticipation of an easier day where they do not have to provide care.
The finding that more daily non-care stressors were associated with higher cortisol levels before bed and probably greater daily total cortisol output was also consistent with previous research on the positive association between daily stressor exposures and naturally occurring cortisol levels (Stawski et al., 2013). However, significant within-person associations between daily stressors and cortisol levels, and slopes were not observed at other sampling occasions, or over the course of the day. One explanation could be the time-dependent nature of HPA axis reactions to daily stressors. Laboratory-induced cortisol levels typically increase 20 - 40 minutes after stressor exposures (Dickerson & Kemeny, 2004). The retrospective stressor report at the end of the day and 5-sample cortisol assessment within a day design utilized in the current study may be less ideal to capture the time-dependent association between stressor exposures and cortisol levels.

Third, the associations between ADS use and cortisol levels and slopes were also between-person, in the context of other daily experiences. More positive experiences were associated with higher cortisol levels 30 minutes after waking. Additionally, more total ADS days during the study period were associated with an increasing cortisol slope starting from late afternoon to before bed. We included that time point specifically because we thought there might be an uptick related to when the IWD comes home. A prior study found total ADS days were also associated with significantly higher cortisol daily total output measured by area under the curve (Klein et al., 2014). The current findings confirmed these results and pinpointed that increased output occurred between dinner and bedtime. This finding again points out the value of spline models versus AUC. While ADS use is able to provide some caregiving respite and decrease care-related stressor exposures (Zarit et al., 2014), it also opens up opportunities for caregivers to engage in a full life, which may have increased the exposures to other non-care
stressors such as work demands as well as positive experiences. The heightened cortisol levels 30 minutes after waking, and the increasing cortisol evening slope reflected in part the increased total stressor exposures associated with greater ADS use.

The study had some limitations. The current daily diary design relied on retrospective self-report on stressor exposures at the end of the day. The salivary cortisol samplings were also intended at relatively fixed time windows. Thus, it was impossible to precisely align the timing of stressors to cortisol samples to accurately track the cortisol diurnal rhythms in association of stressor exposures. This general limitation on naturally occurring cortisol studies can be partially addressed by using a more intense ecological momentary assessment design, where events sampling may be used (Smyth et al., 1998). Also, considering the relatively demanding nature of participating in a daily study, findings based on this sample of dementia caregivers may not be generalizable to a broader population of family caregivers. Further, the study provided some evidence at the daily level that ADS use may be associated with better HPA functioning among caregivers. Future studies need to consider the associations between daily stressor exposures and more than one kind of biomarkers. Additionally, the associations between daily biomarkers and long-term health and well-being need to be explored in the future to better understand the effects of daily stressor exposures on health outcomes.

The study suggested that the four-part linear spline model could best represent the naturally occurring cortisol diurnal trajectory among dementia caregivers who tended to experience a relatively high level of daily stressors. ADS use as a respite had some physiological benefits for dementia caregivers. One pathway through which dementia caregiving compromises health and well-being is through chronic exposures to daily stressors. ADS use provides partial relief from primary stressors of behavior problems on a daily basis, which makes
family caregiving more manageable and may offer caregivers some actual health benefits. Future studies need to focus on the consequences of CAR and the initial morning decline over time. Specifically, testing if these effects are buffered by both daily ADS use and total ADS days used across a period can help fully understand the health effects of respite care on dementia caregivers.
### 2.5 Tables and Figures

Table 1.

*Descriptive statistics for salivary cortisol*

<table>
<thead>
<tr>
<th>Sample collection times</th>
<th>Mean</th>
<th>SD (BP) in minutes</th>
<th>SD (WP) in minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waking</td>
<td>06:45 h</td>
<td>62</td>
<td>43</td>
</tr>
<tr>
<td>30-min after waking</td>
<td>07:19 h</td>
<td>62</td>
<td>43</td>
</tr>
<tr>
<td>Before lunch</td>
<td>12:49 h</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Late afternoon</td>
<td>17:27 h</td>
<td>54</td>
<td>42</td>
</tr>
<tr>
<td>Before bed</td>
<td>22:41 h</td>
<td>62</td>
<td>36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample levels (nmol/l)</th>
<th>Mean</th>
<th>SD (BP)</th>
<th>SD (WP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waking</td>
<td>9.19</td>
<td>4.02</td>
<td>3.93</td>
</tr>
<tr>
<td>30-min after waking</td>
<td>12.32</td>
<td>4.74</td>
<td>4.78</td>
</tr>
<tr>
<td>Before lunch</td>
<td>4.02</td>
<td>1.97</td>
<td>1.81</td>
</tr>
<tr>
<td>Late afternoon</td>
<td>3.04</td>
<td>2.65</td>
<td>1.89</td>
</tr>
<tr>
<td>Before bed</td>
<td>2.77</td>
<td>2.87</td>
<td>2.17</td>
</tr>
</tbody>
</table>

*Notes.* SD (BP) = standard deviation between person; SD (WP) = standard deviation within person across days
### Table 2.

**Salivary cortisol levels and associations with daily experiences and caregiving characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Waking</th>
<th>30-min after Waking</th>
<th>Before Lunch</th>
<th>Late Afternoon</th>
<th>Before Bed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
</tr>
<tr>
<td>Intercept</td>
<td>9.17 (0.35)</td>
<td>11.67 (0.42)</td>
<td>3.97 (0.18)</td>
<td>3.11 (0.23)</td>
<td>2.89 (0.26)</td>
</tr>
<tr>
<td><strong>Within-person covariates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily ADS use</td>
<td>0.01 (0.33)</td>
<td>1.21 (0.39)**</td>
<td>0.11 (0.18)</td>
<td>-0.15 (0.22)</td>
<td>-0.26 (0.29)</td>
</tr>
<tr>
<td>Daily positive experience</td>
<td>0.13 (0.15)</td>
<td>-0.14 (0.18)</td>
<td>0.01 (0.08)</td>
<td>-0.05 (0.10)</td>
<td>-0.06 (0.13)</td>
</tr>
<tr>
<td>Daily non-care stressors</td>
<td>0.03 (0.16)</td>
<td>0.12 (0.18)</td>
<td>-0.06 (0.08)</td>
<td>-0.02 (0.10)</td>
<td>0.30 (0.14)*</td>
</tr>
<tr>
<td>Daily care-related stressors</td>
<td>-0.01 (0.04)</td>
<td>-0.02 (0.05)</td>
<td>-0.03 (0.02)</td>
<td>0.01 (0.03)</td>
<td>-0.04 (0.04)</td>
</tr>
<tr>
<td>Daily sleep quality</td>
<td>0.08 (0.19)</td>
<td>-0.02 (0.22)</td>
<td>-0.09 (0.10)</td>
<td>-0.41 (0.12)***</td>
<td>0.13 (0.16)</td>
</tr>
<tr>
<td>Daily sleep duration</td>
<td>-0.17 (0.20)</td>
<td>-0.26 (0.23)</td>
<td>-0.25 (0.10)*</td>
<td>0.02 (0.13)</td>
<td>-0.15 (0.17)</td>
</tr>
<tr>
<td>Daily wake-up time</td>
<td>0.39 (0.25)</td>
<td>-0.24 (0.29)</td>
<td>0.34 (0.13)**</td>
<td>0.10 (0.16)</td>
<td>0.25 (0.22)</td>
</tr>
<tr>
<td><strong>Between-person covariates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ADS days</td>
<td>-0.12 (0.23)</td>
<td>-0.48 (0.27)</td>
<td>-0.03 (0.11)</td>
<td>-0.02 (0.15)</td>
<td>0.21 (0.16)</td>
</tr>
<tr>
<td>Caregiver age</td>
<td>0.07 (0.03)*</td>
<td>0.06 (0.04)</td>
<td>0.02 (0.02)</td>
<td>0.04 (0.02)*</td>
<td>0.03 (0.02)</td>
</tr>
<tr>
<td>Caregiver gender</td>
<td>-1.09 (0.96)</td>
<td>0.38 (1.13)</td>
<td>-1.03 (0.47)*</td>
<td>-0.71 (0.62)</td>
<td>-0.76 (0.66)</td>
</tr>
<tr>
<td>Duration of care</td>
<td>0.00 (0.01)</td>
<td>0.01 (0.01)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>-0.01 (0.00)</td>
</tr>
<tr>
<td>IWD's ADL dependency</td>
<td>0.79 (0.66)</td>
<td>0.91 (0.79)</td>
<td>0.38 (0.32)</td>
<td>0.92 (0.43)*</td>
<td>0.62 (0.46)</td>
</tr>
<tr>
<td>Average positive experience</td>
<td>0.66 (0.35)</td>
<td>0.96 (0.42)*</td>
<td>0.21 (0.17)</td>
<td>0.32 (0.23)</td>
<td>0.17 (0.24)</td>
</tr>
<tr>
<td>Average non-care stressors</td>
<td>-0.28 (0.41)</td>
<td>-0.44 (0.48)</td>
<td>-0.29 (0.20)</td>
<td>-0.23 (0.26)</td>
<td>-0.05 (0.28)</td>
</tr>
<tr>
<td>Average care-related</td>
<td>-0.02 (0.05)</td>
<td>-0.03 (0.06)</td>
<td>0.03 (0.02)</td>
<td>0.00 (0.03)</td>
<td>-0.01 (0.04)</td>
</tr>
<tr>
<td>Average sleep quality</td>
<td>-0.02 (0.46)</td>
<td>0.25 (0.54)</td>
<td>0.28 (0.22)</td>
<td>0.23 (0.30)</td>
<td>0.36 (0.32)</td>
</tr>
<tr>
<td>Average sleep duration</td>
<td>-0.90 (0.37)*</td>
<td>-0.96 (0.44)*</td>
<td>-0.44 (0.18)*</td>
<td>-0.60 (0.24)*</td>
<td>-0.50 (0.26)*</td>
</tr>
<tr>
<td>Average wake-up time</td>
<td>-0.05 (0.34)</td>
<td>-0.45 (0.41)</td>
<td>0.04 (0.17)</td>
<td>0.03 (0.22)</td>
<td>-0.50 (0.24)*</td>
</tr>
</tbody>
</table>

*Notes.* All daily (within-person) covariates were person-mean centered. All between-person covariates were grand-mean centered. ADS = Adult day services. *p ≤ .05, **p ≤ .01, ***p ≤ .001.
Table 3.

Model comparison among three unconditional spline models on cortisol diurnal trajectory

<table>
<thead>
<tr>
<th>Model</th>
<th>Linear spline model</th>
<th>Linear-quadratic spline model</th>
<th>Linear-cubic spline model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Estimate (s.e.)</strong></td>
<td><strong>Estimate (s.e.)</strong></td>
<td><strong>Estimate (s.e.)</strong></td>
</tr>
<tr>
<td>Intercept</td>
<td>9.18 (0.32)***</td>
<td>9.18 (0.32)***</td>
<td>9.18 (0.32)***</td>
</tr>
<tr>
<td><strong>4-part piecewise linear model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR slope</td>
<td>6.32 (0.59)***</td>
<td>5.52 (0.49)***</td>
<td>6.22 (0.50)***</td>
</tr>
<tr>
<td>1st linear decline slope from 30min after waking to before lunch (AD1)</td>
<td>-1.83 (0.08)***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd linear decline slope from before lunch to late afternoon (AD2)</td>
<td>-0.25 (0.04)***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd linear decline slope from late afternoon to before bed (AD3)</td>
<td>0.07 (0.03)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quadratic and cubic spline model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear decline slope from 30min after waking throughout the day (AD)</td>
<td>-1.68 (0.04)***</td>
<td>-2.50 (0.08)***</td>
<td></td>
</tr>
<tr>
<td>Quadratic decline slope from 30min after waking throughout the day (AD^2)</td>
<td>0.07 (0.00)***</td>
<td>0.21 (0.01)***</td>
<td></td>
</tr>
<tr>
<td>Cubic decline slope from 30min after waking throughout the day (AD^3)</td>
<td></td>
<td>-0.01 (0.00)***</td>
<td></td>
</tr>
<tr>
<td>REML deviance</td>
<td>32959.3</td>
<td>33378.1</td>
<td>33245.7</td>
</tr>
<tr>
<td>AIC</td>
<td>32993.3</td>
<td>33402.1</td>
<td>33271.7</td>
</tr>
<tr>
<td>BIC</td>
<td>33045.4</td>
<td>33438.9</td>
<td>33311.5</td>
</tr>
</tbody>
</table>

Notes. All daily (within-person) covariates were person-mean centered. All between-person covariates were grand-mean centered.

*p ≤ .05, **p ≤ .01, ***p ≤ .001.
Table 4.

Effect of ADS use on diurnal cortisol slopes covarying for daily experiences and caregiving characteristics using linear spline model

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily ADS effect model</td>
<td>Total ADS days effect model</td>
<td>ADS effect full model</td>
</tr>
<tr>
<td><strong>Estimate (s.e.)</strong></td>
<td><strong>Estimate (s.e.)</strong></td>
<td><strong>Estimate (s.e.)</strong></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>9.25 (0.34)***</td>
<td>9.18 (0.32)***</td>
<td>9.31 (0.33)</td>
</tr>
<tr>
<td>CAR</td>
<td>4.40 (0.67)***</td>
<td>6.11 (0.58)***</td>
<td>4.35 (0.67)</td>
</tr>
<tr>
<td>AD1, the first linear decline slope</td>
<td>-1.52 (0.07)***</td>
<td>-1.64 (0.07)***</td>
<td>-1.51 (0.08)</td>
</tr>
<tr>
<td>AD2, the second linear decline</td>
<td>-0.01 (0.07)</td>
<td>-0.07 (0.05)</td>
<td>-0.03 (0.07)</td>
</tr>
<tr>
<td>AD3, the third linear decline slope</td>
<td>-0.08 (0.05)</td>
<td>-0.06 (0.03)</td>
<td>-0.05 (0.05)</td>
</tr>
<tr>
<td><strong>Daily ADS use (1 = ADS day)</strong></td>
<td>-0.13 (0.24)</td>
<td></td>
<td>-0.26 (0.25)</td>
</tr>
<tr>
<td>CAR*ADS</td>
<td>3.26 (0.65)***</td>
<td></td>
<td>3.43 (0.66)***</td>
</tr>
<tr>
<td>AD1*ADS</td>
<td>-0.22 (0.07)***</td>
<td></td>
<td>-0.24 (0.07)***</td>
</tr>
<tr>
<td>AD2*ADS</td>
<td>-0.13 (0.08)</td>
<td></td>
<td>-0.09 (0.10)</td>
</tr>
<tr>
<td>AD3*ADS</td>
<td>0.05 (0.06)</td>
<td></td>
<td>0.00 (0.07)</td>
</tr>
<tr>
<td><strong>Total ADS days</strong></td>
<td></td>
<td>-0.01 (0.22)</td>
<td>-0.04 (0.22)</td>
</tr>
<tr>
<td>CAR*ADS days</td>
<td>-0.11 (0.41)</td>
<td>-0.52 (0.42)</td>
<td></td>
</tr>
<tr>
<td>AD1*ADS days</td>
<td>0.04 (0.05)</td>
<td>0.07 (0.05)</td>
<td></td>
</tr>
<tr>
<td>AD2*ADS days</td>
<td>-0.06 (0.03)</td>
<td>-0.05 (0.03)</td>
<td></td>
</tr>
<tr>
<td>AD3*ADS days</td>
<td>0.07 (0.02)**</td>
<td>0.07 (0.02)**</td>
<td></td>
</tr>
<tr>
<td><strong>Within-person covariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily positive experience</td>
<td></td>
<td>-0.04 (0.07)</td>
<td></td>
</tr>
<tr>
<td>Daily non-care stressors</td>
<td></td>
<td>0.09 (0.07)</td>
<td></td>
</tr>
<tr>
<td>Daily care-related stressors</td>
<td></td>
<td>-0.01 (0.02)</td>
<td></td>
</tr>
<tr>
<td>Daily sleep quality</td>
<td>-0.01 (0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily sleep duration</td>
<td>-0.15 (0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily wake-up time</td>
<td>0.02 (0.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Between-person covariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average positive experience</td>
<td>0.17 (0.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average non-care stressors</td>
<td>-0.11 (0.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average care-related stressors</td>
<td>0.00 (0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average sleep quality</td>
<td>0.26 (0.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average sleep duration</td>
<td>-0.44 (0.18)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average wake-up time</td>
<td>-0.29 (0.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver age</td>
<td>0.03 (0.02)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver gender</td>
<td>-0.65 (0.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of care</td>
<td>0.00 (0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWD’s ADL dependency</td>
<td>0.56 (0.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REML deviance</td>
<td>33000.5</td>
<td>33039.8</td>
<td>33049.6</td>
</tr>
<tr>
<td>AIC</td>
<td>33024.5</td>
<td>33063.8</td>
<td>33065.6</td>
</tr>
<tr>
<td>BIC</td>
<td>33061.2</td>
<td>33100.6</td>
<td>33090.1</td>
</tr>
</tbody>
</table>

**Notes.** ADS = Adult day services.
All daily (within-person) covariates were person-mean centered. All between-person covariates were grand-mean centered.
The linear spline model (Model A in Table 3) was used for all three models.
Model 1 tested the daily ADS effect.
Model 2 tested the total ADS days effect.
Model 3 was the full model, controlling for covariates of daily experiences and caregiving characteristics.
Nonsignificant interactions between daily experiences and cortisol slopes were trimmed from Model 3.
*p ≤ .05, **p ≤ .01, ***p ≤ .001.
Figure 1. *Diurnal salivary cortisol curves based on the three unconditional models*

Note. Cortisol levels were measured in nmol/l.
CAR is the common slope in all three models.
AD1, AD2, and AD3 are the three linear decline slopes in Model A.
AD and AD^2 are the linear and quadratic decline slopes in Model B.
AD, AD^2 and AD^3 are the linear, quadratic and cubic slopes in Model C.
Figure 2. The effect of daily ADS use on salivary cortisol diurnal slopes

Note. Cortisol levels were measured in nmol/l.
CHAPTER 3. STUDY 2.

*Diurnal Salivary Alpha-amylase Dynamics among Dementia Family Caregivers: Daily Stressors and Adult Day Services Use*

3.1 Background and Literature Review

Family caregiving to individuals with dementia (IWDs), which is usually sustained for years, has been found to be both physically and emotionally challenging (Aneshensel, Pearlin, Mullan, Zarit, & Whitlatch, 1995). The chronicity of helping IWDs with daily, recurrent tasks can take a toll on caregivers. Prior inquiries on caregivers have typically shown evidence of compromised health and well-being. From a theoretical perspective (Pearlin, Mullan, Semple, & Skaff, 1990), both objective behavioral and psychological symptoms of dementia and subjective appraisal of such symptoms create a rich context for exposure to intense and chronic stress. Not surprisingly, epidemiologic studies reveal that caregivers of IWDs are at high risk for health problems and depression (Aneshensel et al., 1995; Pinquart & Sörensen, 2003b).

**Caregiving and the biobehavioral stress response**

Contemporary theories suggest that individual differences in the reactivity and regulation of biobehavioral stress responses moderate the link between caregiving stress and risk for negative health outcomes. Two major components of the stress response involve activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) (Chrousos & Gold, 1992). This activation results in key biomarkers of HPA-axis and SNS activity, which can be measured non-invasively in saliva, such as salivary cortisol and salivary alpha-amylase (sAA) respectively (Granger, Kivlghan, El-Sheikh, Gordis, & Stroud, 2007).
Savla, Roberto, Blieszner, Cox, and Gwazdauskas (2011) examined psychological and behavioral problems of persons with mild cognitive impairment and associations with spouse caregiver well-being. On days when primary stressors such as memory problems and sundowning effect were experienced, caregivers reported higher levels of negative and lower levels of positive affect. Caregivers also reported more distress on days when non-care stressors such as unpleasant interactions with their spouses were experienced. Further, caregivers had more pronounced cortisol awakening responses, shallow-declining cortisol slopes and higher total cortisol output throughout the day when they reported encountering patient behavior problems. In a more recent study on the same sample, Savla and colleagues (2013) confirmed that daily objective stressors were associated with higher cortisol levels and a flatter cortisol diurnal slope, and unpleasant marital interactions were associated with flatter diurnal sAA slopes.

The daily stress of caregiving

Pearlin’s stress process model (Pearlin et al., 1990) conceptualizes caregiver health and well-being as consequences of multidimensional processes, including primary stressor exposures – the actual caregiving challenges, and how caregivers appraise and respond to these primary stressors; and other extrinsic stressors in a broader social context. Specifically, depending on caregivers’ resources and general life situations, caregiving can have heterogeneous consequences on caregiver well-being. To have a more refined understanding of what factors determine why some caregivers fare well while others do not, recent studies have utilized daily diaries to uncover the dynamics and pathways in caregiver health and well-being.
The stress process model extends naturally to the daily context of caregiving and non-care experiences. Daily diaries afford an up-close perspective on daily experiences, which show that minor but frequent caregiving challenges on a daily basis may have immediate consequences on caregiver health (i.e., Savla, Almeida, Davey, & Zarit, 2008). The most common daily stressor is IWDs’ behavioral and psychological symptoms, such as wandering, agitation, and resistance. Such behavior problems can pose considerable challenges to caregivers on a daily basis, which lead to heightened negative feelings such as burden, overload, captivity, and loss of intimate exchange. Daily positive events, on the other hand, may be associated with improved positive affect and enhanced well-being (Zarit, Kim, Femla, Almeida, & Klein, 2014).

**Salivary alpha-amylase: An indicator of SNS reactivity and regulation**

Salivary alpha-amylase (sAA) is a well characterized non-invasive surrogate marker of SNS reactivity and regulation (Granger et al., 2007; Nater & Rohleder, 2009; Piazza, Almeida, Dmitrieva, & Klein, 2010). sAA is unique from most other common salivary biomarkers in that it is not transported actively or diffused passively into saliva from the general circulation. sAA is produced in the oral cavity by the salivary glands in response to SNS stimulation. As an enzyme, the main function of sAA is carbohydrate digestion (Rohleder & Nater, 2009). sAA appears to be a viable stress marker as it parallels increases in SNS-induced release of norepinephrine, a stress hormone associated with SNS activation (Rohleder & Nater, 2009). Studies in the laboratories showed that sAA levels increase in response to caffeine administration and acute stressors such as physical exercise, heat and cold stress, the Trier Social Stress Test, and psychosocial stressors such as taking examinations and competitions (see Klein et al., 2010; Nater & Rohleder, 2009 for reviews).
Prior studies have also suggested interesting associations between sAA levels and physical health problems. It was reported that poor sAA recovery from pre- to post-stress conditions were associated with increased health problems such as fatigue, respiratory problems, and frequency of illness among children as reported by parents and teachers (Granger et al., 2007). Granger and colleagues (2007) also found that sAA levels were positively associated with SIgA, an antibody playing a critical role in mucosal immune protection against upper respiratory infection, during post-challenge conditions and recovery from pre- to post-challenge conditions.

Caregiver studies incorporating sAA as an outcome measure typically have revealed the physiological toll of caregiving. Rohleder and colleagues (2009) collected saliva and blood samples from 18 caregivers (mean age = 50.4) of patients with brain cancer after diagnosis and 19 controls (mean age = 50.2). Caregivers reported more perceived stress and more depressed mood than controls, which persisted over time at a similar level. Although the diurnal rhythm of sAA did not differ between caregivers and controls at baseline, caregivers showed a decreasing-and-increasing pattern over time in diurnal output of sAA, which paralleled the timing of patient radiotherapy. Specifically, during the most stressful period of radiotherapy, caregivers’ sAA showed a less pronounced increase in the early afternoon, and lower levels throughout the day. The control group had stable sAA levels during follow-up. Furthermore, the changes in caregiver sAA profile were accompanied by a profound increase in systemic inflammation, which may place caregivers at risk for morbidity and mortality. Similarly, Savla and colleagues (2013) examined care-related stressors of behavior problems from spouses with mild cognitive impairment (MCI) and unpleasant interactions with spouses; they also examined 30 caregivers’ (age range was 59 to 85) diurnal patterns of sAA on 4 consecutive days. A flatter declining
slope of sAA was associated with unpleasant interactions, but not behavior problems, which included mood disturbances, memory issues, and restless behaviors. These studies in naturalistic settings suggested that chronic stressors were associated with lower levels of sAA, lower daily output, and flattened diurnal rhythms (i.e., less pronounced nadir in the morning and less afternoon increase), whereas higher sAA daily output was likely to be associated with older age.

**Adult day services use in relation to caregiving stress and physiology**

One way to alleviate some of the stressor exposures associated with caregiving is through respite use, such as adult day services (ADS). ADS programs provide a predictable amount of time away from the IWDs, creating opportunities for caregivers to engage in other constructive activities and to gain relief from the constant demands associated with care provision. Thus, a caregiver’s day can be filled with higher or lower numbers of stressors, depending on whether it is a non-ADS or ADS day. Sustained ADS use can help lower caregivers’ feelings of overload, worry and strain, and both level and fluctuations of daily depressive symptoms and anger in the short term and over the long run (Liu, Kim, Almeida, & Zarit, 2015; Zarit et al., 2014; Zarit, Stephens, Townsend, & Greene, 1998).

A small number of studies have examined how ADS affects the association between caregiving stressor exposures and the biological stress response. Klein and colleagues (2014) found that caregivers with attenuated cortisol awakening responses (CAR) and low salivary cortisol daily output on non-ADS days tended to have a more normative CAR and daily output on ADS days; whereas caregivers with the highest CAR and greatest daily total output on non-ADS days tended to display a restored cortisol regulation on ADS days. In that same study, Zarit and colleagues (2014) found that levels of salivary dehydroepiandrosterone-sulfate (DHEA-S), an
anabolic steroid that may impart health protective benefits under stress, were significantly higher on days following ADS use, and DHEA-S levels covaried with positive affect on a day-to-day basis. The study suggested that regular ADS use may benefit caregivers’ physiological functioning by increasing DHEA-S levels. However, no studies have examined ADS use in association with daily stressor exposures and sAA regulation in a dementia caregiver sample.

3.2 The current study

Building on prior studies that identified the effects of stressor exposures on sAA diurnal rhythm, the current study examines the typical sAA diurnal trajectory among a sample that experienced the chronic stress of dementia caregiving who also had a relatively high level of daily stressors. Additionally, the study tests whether sAA diurnal slopes are associated with ADS use and other daily experiences. As there are few studies that have examined sAA diurnal rhythms at the daily level, the typical diurnal trajectory of sAA among caregivers was modeled first using unconditional piecewise linear spline growth curves, which have been applied to model cortisol diurnal rhythms (Ranjit, Young, Raghunathan, & Kaplan, 2005). Guided by prior research, a typical sAA trajectory across the day can be represented by a linear decrease during the 30 minutes of awakening, and a gradual increase throughout the day, with a slight decline between late evening and before bed (Nater, Rohleder, Schlotz, Ehlert, & Kirschbaum, 2007).

In the current study, caregivers were observed over 8 consecutive days, using ADS on some days of observation and not others. ADS use represented a manipulation by which exposure to naturally-occurring daily stressors was varied. On ADS days, caregivers have lower care-related stressor exposures (Zarit et al., 2014). The current study tests whether ADS use had any within- (i.e., daily use) and between-person (i.e., total ADS days during the observation period) effects on sAA diurnal rhythms. Then ADS effects were evaluated again after covariates
of daily experiences and caregiving characteristics were added into the model. The current study tested first at the within-person level whether daily ADS use could impact sAA diurnal slopes across high- versus low-stressor days. Additionally, the study examined whether there is any between-person ADS effect (i.e., total ADS days during the observation period) on sAA diurnal trajectories. Finally, the study examined if there is any association between sAA diurnal slopes and daily stressor exposures at both within- (i.e., daily exposure) and between-person levels (i.e., average exposure across days), in the context of ADS use. Specifically, the current study has the following hypotheses on ADS use and daily stressor exposures.

**Hypothesis 1:** Daily ADS use will be associated with sAA diurnal slopes at the within-person level. Specifically, on non-ADS days when care-related stressors are relatively high, caregivers will have attenuated or flattened diurnal slopes, controlling for daily experiences (non-care stressors and positive events) and other caregiving characteristics. On ADS days when care-related stressors are relatively low, however, caregivers may have a steeper diurnal pattern for sAA slopes.

**Hypothesis 2:** Total ADS days across the observation period will be associated with sAA diurnal slopes at the between-person level. Specifically, more ADS days will be associated with a more pronounced diurnal pattern for sAA diurnal slopes.

**Hypothesis 3:** Daily stressor exposures and positive experiences will be associated with sAA diurnal slopes. Specifically, greater stressor exposures may be associated with attenuated or flattened sAA diurnal slopes. More positive experiences, on the other hand, will be associated with more prominent sAA diurnal slopes.

### 3.3 Methods
Participants

Participants were 176 family caregivers who were participating in an 8-day diary study, the Daily Stress and Health (DaSH) study (Zarit et al, 2014). Eligibility for the study included: a) providing primary care to IWDs who lived in the same household, b) reporting the IWD having a type of dementia such as Alzheimer’s disease that was diagnosed by a physician, c) using ADS programs at least two days a week, and d) had no medical problems that limited production of saliva (Zarit, Kim, et al., 2014). Eleven participants (6.3%) who provided daily diaries and sAA samples were excluded from the analysis. Three had mixed up or missed samples (1.7%) and two (1.1%) were sisters who shared care responsibilities equally. An additional six caregivers (3.4%) who only provided a homogeneous set of interviews (i.e., all ADS or all non-ADS days) were also excluded from the analysis. In total, the 165 caregivers provided 6,121 valid sAA samples (95.6% compliance) on 1,281 valid diary days (97.0% compliance). Of these 6,121 samples, 3,183 in total (52%) were collected on ADS days (mean = 4.16, SD = 1.45), and 2,938 in total were collected on days when IWDs were at home with their caregivers (mean = 3.78, SD = 1.43). Demographic characteristics of caregivers and the IWD they were caring for are presented in Table 8.

Procedures

ADS programs were identified through regional and state Adult Day Services associations. Programs that agreed to participate were provided with detailed information about the study, recruitment brochures, and announcements that could be included in the newsletters. Over a 3-year period, family caregivers from 57 ADS programs expressed interest in participation. These caregivers were phoned by the research coordinator, given additional information about the study, and screened for eligibility. Subsequently, an initial face-to-face
interview was conducted at the caregiver’s home, during which they signed consent forms and completed a set of questionnaires. After the initial meeting and baseline assessment, caregivers participated in daily interviews for 8 consecutive days via evening phone calls (conducted by the Penn State Survey Research Center); they also provided saliva samples five times each day. Caregivers received $150 for completing the entire study protocol.

Using previously published methods for saliva collection, participants were instructed to: 1) provide saliva samples at 5 specified times during the day by rolling an absorbent swab across the tongue for 2 minutes, 2) record their saliva collection times, 3) avoid taking samples within 30 minutes of eating, drinking, brushing teeth, using tobacco or caffeinated products, and 4) refrigerate saliva samples until the end of the 8 days (e.g., Klein et al., 2014). Additionally, participants recorded medications taken over the past 48 hours, tobacco smoking status, and, for women, information on hormone status (e.g., menstrual cycle, hormone therapy use).

Instructions for saliva collection were reviewed during an initial in-home interview and in the first phone interview. At the end of the saliva collection period, saliva samples were couriered overnight at room temperature to the Penn State Biomarker Core Lab where they were frozen at -80 degrees C until assay. On testing day, samples were thawed at room temperature and tested for sAA using a commercially available kinetic enzyme reaction assay kit without modification to the manufacturers recommended protocol (Salimetrics, LLC; State College, PA). The sample test volume was 10 ul of saliva. Salivary alpha-amylase measurement units are expressed in U/mL. The assay range of sensitivity was 2 to 400 U/mL, with average inter- and intra-assay coefficients of variation less than 6% and 7.5%, respectively. Per assay protocol, sAA activity was tested for each sample in singlet. Samples were excluded from the analysis if participants were awake for less than 12hr or greater than 20hr ($n = 70$) or woke up after 12pm ($n = 0$).
Samples with missing values \((n = 171)\), too little saliva for assaying \((n = 103)\), or missing time or dates \((n = 10)\) were also excluded from the final analysis. The skewness of sAA samples ranged from 2 to 2.69, which was considered not severe \(\text{e.g., George} \& \text{Mallery, 2010}\). Thus the analysis was done using the original sAA values without any transformation.

**Measures**

**Daily ADS use.** In each daily interview the caregivers indicated whether they had made use of ADS that day. From these reports, both time-varying and time-invariant variables were derived. The time-varying \(\text{i.e., within-person and daily}\) ADS use was a binary variable indicating use \((= \text{1})\) or nonuse \((= \text{0})\) that day. A time-invariant \(\text{i.e., between-person}\) ADS use was computed as the sum of total ADS days across the daily interview period.

**Daily stressors.** Two types of daily stressors were distinguished: care-related stressors and non-care stressors. *Care-related stressors* were considered in relation to the IWD’s daily behavior problems and were measured using the Daily Record of Behavior \(\text{DRB}\). The DRB, designed specifically for use in daily diaries, assesses the frequency with which 19 behaviors occurred over a 24-hour time frame \(\alpha = .78\), see Femia, Zarit, Stephens, \& Greene, 2007 for detailed psychometric properties). To assist caregivers in reporting, the day is broken up into four time-blocks that correspond to the modal periods during which caregivers use ADS: a) waking to 9:00 a.m., b) 9:00 a.m. to 4:00 p.m. \(\text{typical ADS attendance hours}\), c) 4:00 p.m. to bedtime, and d) overnight. For each period of the day, caregivers were asked whether each behavior had occurred \(\text{yes/no}\). From these reports, both time-varying and time-invariant variables were derived. Because overnight stressor exposures were very low, the current study only utilized stressor exposures reported during three day-time windows. The time-varying care-related stressors were the sum of total behavior occurrences reported that day, excluding the
overnight period; the time-invariant care-related stressors were the average level of daily behavior occurrences reported across the interview period.

Caregivers may experience daily stressors in other life domains that are unrelated to caring for their relatives. *Non-care stressors* were measured using the Daily Inventory of Stressful Events (DISE; Almeida, Wethington, & Kessler, 2002). Each evening, caregivers reported on the occurrence (yes/no) of eight events over the previous 24-hour period (α = .59): arguments with other people, whether they avoided an argument with someone, incidents concerning their friends or family, health-related issues or incidents, money or finance-related issues, work-related issues, and other stressful issues or incidents. Separating care-related and non-care stressors, caregivers were specifically instructed to report events they found stressful other than those encountered when assisting their relative. Both time-varying and time-invariant variables were derived based on the daily reports. The time-varying non-care stressors were the sum of stressors reported across all eight categories that day; the time-invariant non-care stressors were the average level of daily stressors reported across the interview period.

**Daily positive events.** Positive experiences were also assessed as they have been found to reduce the effects of stressors on daily affect and physiological responses (e.g., Zarit et al., 2014). Using five items drawn from the DISE (α = .63, Almeida et al., 2002), caregivers reported occurrences of positive experiences during the past 24 hours: sharing a laugh with someone, having an experience at home, with a close friend or relative, or at work that others would consider positive, and any other positive experience. Both time-varying and time-invariant variables based on the daily reports were derived. The time-varying variable was the sum of positive events reported across all five categories that day; the time-invariant variable was the average level of daily positive events across the interview period.
**Covariates.** Additional variables that have been associated with sAA levels were considered as covariates. Caregivers’ chronological age, gender (1 = *female* and 0 = *male*), duration of care provision (*months*), the IWD’s ADL dependency (mean of 13 items; coded on a 4-point scale; 1 = *does not need help* to 4 = *cannot do without help*; higher scores indicated greater dependency; $\alpha = .83$), and caregivers’ sleep quality, assessed each day as the response to the item: “Rate the quality of your sleep last night” (5-point scale; 1 = *poor* to 5 = *excellent*). Caregivers’ daily sleep quality was used as a time-varying covariate and caregivers’ mean sleep quality across days was used as a time-invariant covariate.

**Analytical strategy**

The goal of the analysis was to describe the diurnal rhythm and examine the regularities of naturally-occurring sAA in the daily context. Preliminary analyses were run first using sAA levels at each sampling occasion and daily total output as outcomes. To describe the typical sAA diurnal rhythms among the sample of dementia caregivers, an unconditional four-part piecewise linear spline model was fit with time as the only independent variable. Specifically, daily sAA levels were modeled as functions of time elapsed since wake-up, with knots (where the linear components join in) fixed at 0.5hr, 6hr, 10.5hr and 16hr after wakeup. Fixed knots allowed the timing of the sAA peak to vary across caregivers. These fixed inflection time points reflected the observed average sampling time. A 3-level unconditional model was used to model the sAA diurnal slopes to account for within-day and within-person correlations in sAA levels.

To test all three hypotheses on ADS use and daily stressor exposures, predictors and covariates were added to the unconditional piecewise linear spline model. To test Hypotheses 1 and 2 on within- and between-person effects of ADS use, daily ADS use and total ADS days were added to the unconditional piecewise linear spline model, respectively. ADS effects were
reevaluated after controlling for covariates of other daily experiences and caregiving characteristics. Then this full model were also used to test Hypothesis 3 on effects of daily stressor exposures and positive experiences on sAA diurnal slopes, in the context of ADS use.

The full model was specified such that AD, AR1, AR2 and AR3 represented the four linear slopes of the four-part linear spline model. Specifically, AD was the first linear decline slope from wake-up to 30min after wake-up; AR1 was the first linear rise from 30min after wake-up to before lunch; AR2 was the second linear rise from before lunch to late afternoon, and AR3 the third linear rise from late afternoon to before bed. These four linear slopes were then specified to vary based on within- and between-person ADS use, stressor exposures, and other caregiving characteristics:

Level 1 (Within-day level):
Salivary alpha-amylase_{sdi} = \pi_{0di} + \pi_{1di} (AD1_{sdi}) + \pi_{2di} (AD2_{sdi}) + \pi_{3di} (AD3_{sdi}) + \pi_{4di} (AD4_{sdi}) + \epsilon_{sdi}

Level 2 (Across-day level):
\pi_{0di} = \beta_{00i} + \beta_{01i} (Daily ADS use_{di}) + \beta_{02i} (Daily care-related stressors_{di}) + \beta_{03i} (Daily non-care stressors_{di}) + \beta_{04i} (Daily positive events_{di}) + \beta_{05i} (Daily sleep quality_{di}) + \nu_{0di}
\pi_{1di} = \beta_{10i} + \beta_{11i} (Daily ADS use_{di}) + \beta_{12i} (Daily care-related stressors_{di}) + \beta_{13i} (Daily non-care stressors_{di}) + \beta_{14i} (Daily positive events_{di}) + \nu_{1di}
\pi_{2di} = \beta_{20i} + \beta_{21i} (Daily ADS use_{di}) + \beta_{22i} (Daily care-related stressors_{di}) + \beta_{23i} (Daily non-care stressors_{di}) + \beta_{24i} (Daily positive events_{di}) + \nu_{2di}
\pi_{3di} = \beta_{30i} + \beta_{31i} (Daily ADS use_{di}) + \beta_{32i} (Daily care-related stressors_{di}) + \beta_{33i} (Daily non-care stressors_{di}) + \beta_{34i} (Daily positive events_{di}) + \nu_{3di}
\pi_{4di} = \beta_{40i} + \beta_{41i} (Daily ADS use_{di}) + \beta_{42i} (Daily care-related stressors_{di}) + \beta_{43i} (Daily non-care stressors_{di}) + \beta_{44i} (Daily positive events_{di}) + \nu_{4di}

Level 3 (Between-person level):
\beta_{00i} = \gamma_{000} + \gamma_{001} (Total ADS days_{i}) + \gamma_{002} (Average care-related stressors_{i}) + \gamma_{003} (Average non-care stressors_{i}) + \gamma_{004} (Average positive events_{i}) + \gamma_{005} (Average sleep quality_{i}) + \gamma_{006} (Gender_{i}) + \gamma_{007} (Duration of care_{i}) + \gamma_{008} (IWD’s ADL dependency_{i}) + \gamma_{009} (Age_{i}) + u_{00i}
\beta_{01i} = \gamma_{010}
\vdots
\beta_{05i} = \gamma_{050}
\[ \beta_{10i} = \gamma_{100} + \gamma_{101} \text{(Total ADS days}_i) + \gamma_{102} \text{(Average care-related stressors}_i) + \gamma_{103} \text{(Average non-care stressors}_i) + \gamma_{104} \text{(Average positive events}_i) + \gamma_{105} \text{(Average sleep quality}_i) + \gamma_{106} \text{(Gender}_i) + \gamma_{107} \text{(Duration of care}_i) + \gamma_{108} \text{(IWD’s ADL dependency}_i) + \gamma_{109} \text{(Age}_i) + u_{10i} \\
\beta_{11i} = \gamma_{110} \\
\beta_{12i} = \gamma_{120} \\
\beta_{13i} = \gamma_{130} \\
\beta_{14i} = \gamma_{140} \\
\beta_{20i} = \gamma_{200} + \gamma_{201} \text{(Total ADS days}_i) + \gamma_{202} \text{(Average care-related stressors}_i) + \gamma_{203} \text{(Average non-care stressors}_i) + \gamma_{204} \text{(Average positive events}_i) + \gamma_{205} \text{(Average sleep quality}_i) + \gamma_{206} \text{(Gender}_i) + \gamma_{207} \text{(Duration of care}_i) + \gamma_{208} \text{(IWD’s ADL dependency}_i) + \gamma_{209} \text{(Age}_i) + u_{20i} \\
\beta_{21i} = \gamma_{210} \\
\beta_{22i} = \gamma_{220} \\
\beta_{23i} = \gamma_{230} \\
\beta_{24i} = \gamma_{240} \\
\beta_{30i} = \gamma_{300} + \gamma_{301} \text{(Total ADS days}_i) + \gamma_{302} \text{(Average care-related stressors}_i) + \gamma_{303} \text{(Average non-care stressors}_i) + \gamma_{304} \text{(Average positive events}_i) + \gamma_{305} \text{(Average sleep quality}_i) + \gamma_{306} \text{(Gender}_i) + \gamma_{307} \text{(Duration of care}_i) + \gamma_{308} \text{(IWD’s ADL dependency}_i) + \gamma_{309} \text{(Age}_i) + u_{30i} \\
\beta_{31i} = \gamma_{310} \\
\beta_{32i} = \gamma_{320} \\
\beta_{33i} = \gamma_{330} \\
\beta_{34i} = \gamma_{340} \\
\beta_{40i} = \gamma_{400} + \gamma_{401} \text{(Total ADS days}_i) + \gamma_{402} \text{(Average care-related stressors}_i) + \gamma_{403} \text{(Average non-care stressors}_i) + \gamma_{404} \text{(Average positive events}_i) + \gamma_{405} \text{(Average sleep quality}_i) + \gamma_{406} \text{(Gender}_i) + \gamma_{407} \text{(Duration of care}_i) + \gamma_{408} \text{(IWD’s ADL dependency}_i) + \gamma_{409} \text{(Age}_i) + u_{40i} \\
\beta_{41i} = \gamma_{410} \\
\beta_{42i} = \gamma_{420} \\
\beta_{43i} = \gamma_{430} \\
\beta_{44i} = \gamma_{440} \\

3.4 Results

Descriptives of individual sAA samples, including the collection time, levels, and the ICC on each individual sample across days, are presented in Table 5. Substantial variation in sampling time and levels was observed. Preliminary analyses were run using each individual sample and daily total output calculated as area under the curve with respect to ground (AUCg)
as outcomes (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The purpose of these models was to examine associations between sAA levels and daily stressor exposure as well as effects of caregiving characteristics. Parameter estimates from these models are presented in Table 6. The models showed no within-person (i.e., daily) ADS effect. However, between-person ADS use (i.e., total ADS days) had significant associations with sAA levels from three sampling occasions, and the daily total output as measured by AUCg. Specifically, more ADS days were associated with higher levels and greater daily output. Additionally, better sleep quality the previous night was associated with lower sAA levels before lunch; more daily care-related stressors were associated with lower sAA levels in the late afternoon.

Next, to describe the typical diurnal sAA rhythm, a 3-level unconditional piecewise linear spline model was fit. Parameter estimates are presented for Model 1 in Table 7. The typical diurnal sAA rhythm was graphed in Figure 3, based on parameter estimates from the unconditional model. The model showed that waking sAA level was about 140.26 U/mL, which dropped sharply at a rate of 109.56 U/mL per hour within 30 minutes after awakening. Then sAA levels gradually increased at a rate of 14.86 U/mL per hour between 30 minutes after awakening and before lunch. After a stable period between before lunch and late afternoon, sAA decreased slightly at a rate of 1.51 U/mL per hour between late afternoon and before bed.

To test the hypotheses on within- and between-person ADS use and diurnal sAA regulations, two models were fit. Daily ADS use and total ADS days were tested in the unconditional linear spline model respectively, for their main effects and interactions with each of the sAA linear slopes. Parameter estimates are presented for Model 2 and 3 in Table 7. Hypothesis 1 on daily ADS use was not supported, as Model 2 showed no significant interactions of ADS versus non-ADS days with any of the sAA slopes. Hypothesis 2 concerning total ADS
days was supported. Model 3 showed that, controlling for daily ADS use, more ADS days were associated with a more prominent rise between 30 minutes after awakening and before lunch ($\beta = 1.99, p = 0.03$), as well as a more prominent decline between before lunch and late afternoon ($\beta = -2.22, p = 0.02$). Fewer ADS days, on the other hand, were associated with a more flattened sAA diurnal rhythm. This pattern of association between diurnal sAA slopes and total ADS days was graphed in Figure 4.

Finally, a full model was fit with daily stressor exposures and positive experiences, along with within- and between-person ADS effects. The purpose of this full model was to test the third hypothesis on associations between sAA diurnal slopes and daily experiences in the context of ADS use. Nonsignificant effects were trimmed from the final model, and parameter estimates are presented for Model 4 in Table 7. Hypothesis 3 was supported partially. First, care-related stressors had within- and between-person associations with sAA diurnal slopes. Specifically, at the within-person level, more daily care-related stressors were associated with less rise in sAA levels between 30 minutes after awakening and before lunch ($\beta = -0.36, p = 0.048$); they were also associated with increasing sAA levels between late afternoon and before bed ($\beta = 0.17, p = 0.03$). At the between-person level, more average care-related stressors were associated with increasing sAA levels between late afternoon and before bed ($\beta = 0.17, p = 0.01$). Furthermore, daily positive experiences had a significant between-person association with sAA diurnal slopes only. Specifically, more average positive experiences were associated with increasing sAA levels between late afternoon and before bed ($\beta = 1.04, p = 0.01$). There were no significant associations found for daily non-care stressors.

3.5 Discussion
The study is among the first to examine sAA diurnal rhythms and the effect of a respite intervention among a sample of dementia family caregivers in the context of daily experiences. The study is unique in many ways. First, participants are experiencing chronic stress, with the majority of the participants providing care for more than one year and less than five years. About a third of the participants have provided care for more than 5 years. In addition to the chronic stress of caregiving, these caregivers also tend to experience a relatively high levels of daily stressors. Second, the study utilized a daily diary design, where caregivers self-reported their daily experiences and provided multiple daily saliva samples across eight days. Such a design is ideal to examine both within- and between-person associations between stressor exposures and health, which has been measured by salivary biomarkers. Third, the respite intervention of day care use was incorporated into the daily design, providing a manipulation on naturally-occurring daily stressor exposures. Thus, it was possible to test if there was any ADS effect on sAA as the high versus low-stress days unfold. Finally, sAA regulation was examined from multiple perspectives of daily levels, daily total output, and diurnal slopes. The sAA diurnal slopes were modeled using a piecewise growth curve approach, which has previously been applied to cortisol diurnal rhythms, but has had limited application in studying sAA diurnal regulations.

The primary purposes of the study were to evaluate the associations between daily stressor exposures and sAA regulation, and to test if there was any ADS effect on participants’ naturally-occurring sAA diurnal profiles in the daily caregiving context. In terms of sAA daily levels, greater daily care-related stressor exposures had a within-person association with lower sAA levels in the late afternoon. Additionally, care-related stressor exposures had significant within- and between-person associations with sAA diurnal slopes. At the within-person level,
more daily care-related stressors were related to a blunted rise between 30 minutes after awakening and before lunch. At both the within- and between-person levels, more daily and average care-related stressors were related to a greater rise between late afternoon and before bed.

These findings on stressor exposures and sAA levels seem to contradict prior research by Nater et al. (2007), where chronic stress was associated with higher average sAA levels across the day. Possible explanations are that their sample of participants were healthier and much younger (mean age was about 27) than the current sample; those participants were not experiencing significant chronic stress as measured by the Chronic Stress Screening Scale upon entering the study, either. The current findings, however, were consistent with a prior caregiving study (Rohleder et al., 2009). That study compared cancer caregivers (mean age was about 50) with a comparison group of non-caregivers. Caregivers had significantly higher perceived stress and depressed mood than the control group. Rohleder and colleagues (2009) also found that during the most stressful period of patient radiotherapy, caregivers showed attenuated sAA patterns with decreased secretion. Specifically, sAA levels were lower in the afternoon, and their sAA diurnal slopes showed a less pronounced rise in the late morning than the controls. Further, the sAA daily total output was steadily increasing among the controls over time, whereas the caregivers had relatively stable output during the study period. These findings confirmed that the chronic stress of caregiving was likely to be associated with an attenuated sAA profile, which reflects the physiological toll of care. Thus, caring for a disabled family member may heighten the vulnerability to potential physical and psychological conditions.

The physiological benefits of ADS use on sAA regulation were in two ways. More ADS days were associated with higher sAA levels in three daily sampling occasions (e.g., 30min after
waking, before lunch, and before bed). More ADS days were also associated with higher daily total output. In terms of ADS effect on the sAA diurnal slopes, the study revealed a robust significant between-person association. Specifically, more ADS days were related to a more prominent rise in sAA levels between 30 minutes after awakening and before lunch, and a more prominent decline in sAA levels between before lunch and late afternoon. It is probable that more ADS days can shield a greater amount of care-related stressor exposures cumulatively, thus the physiological toll of caregiving is not as severe among caregivers who utilized ADS to a greater extent. Rohleder and colleagues (2009) proposed a similar mechanism between stressor exposure and sAA regulation. The current study did not show, however, any within-person association between daily ADS use and sAA diurnal regulation processes, even though ADS use lowered care-related stressor exposure. The absence of a specific within-person effect of ADS may be due to the fast-reacting nature of sAA to stressor exposures and experiences (Granger et al., 2007).

Interestingly, there was a significant association between greater average positive experiences and a steeper sAA slope between late afternoon and before bed. A similar association was also found for daily and average care-related stressors in the same time window during the day. The fact that the SNS is not valence specific, and its arousal is associated with either positive or negative emotions which is driving the reactivity of sAA has been noted in the past research. Adam, Hoyt, & Granger (2011) found that high arousal positive (i.e., feeling excited) and negative emotions (i.e., feeling stressed) were associated with acute sAA increases among youth who had high average levels of these emotions. Thus sAA increases may reflect emotional arousal in levels of both positive and negative valence. Thus the pattern of findings among caregivers in the current study is not surprising.
The study has some limitations. Information on self-reported stressor exposures and positive experiences was collected once at the end of the day. Although the daily diary approach reduces retrospective recall errors compared to use of longer recall periods, the design cannot precisely align stressor exposures with sAA levels within a day. This is a drawback, especially considering sAA tends to react relatively quickly in response to stressor exposures compared with other kinds of biomarkers such as salivary cortisol (Nater et al., 2006). This limiting feature of the study may be responsible for the nonsignificant association between daily non-care stressors and sAA regulations. Also, the study considered a single biomarker of sAA, which mainly reflects stressor reactivity of the SNS. Future studies may consider the synchrony of more than one kind of biomarkers to elucidate the impact of stressors on multiple bodily systems. Further, the study did not control for medication use among caregivers. Some medication taken at specific time may have directly affected the SNS, influencing the sAA diurnal within and between caregivers.

In conclusion, the study expands the scientific understanding on chronic stressor exposures and sAA diurnal regulations. Most importantly, consistent with reports of other studies (Klein et al., 2014; Zarit, Whetzel, et al., 2014) the findings suggest that regular ADS use may have some physiological benefits, which might mitigate the physical toll typically associated with dementia caregiving. Caregiving respite such as ADS use can provide partial but invaluable relief from daily care-related stressor exposures, which can make caregiving more manageable and reduce caregivers’ health risks. Further studies are needed to evaluate the ADS effects from a within-person perspective (i.e., daily ADS use) on other biomarkers and health outcome measures in order to fully realize the broad benefits of respite care on dementia caregiver health and well-being in the long run.
### 3.6 Tables and Figures

**Table 5**

*Dailly salivary alpha-amylase sample descriptives*

<table>
<thead>
<tr>
<th>Collection time</th>
<th>Level (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td></td>
</tr>
<tr>
<td>Waking</td>
<td>6.44 h</td>
</tr>
<tr>
<td>30 min after waking</td>
<td>7.23 h</td>
</tr>
<tr>
<td>Before lunch</td>
<td>12.50 h</td>
</tr>
<tr>
<td>Late afternoon</td>
<td>17.28 h</td>
</tr>
<tr>
<td>Before bed</td>
<td>22.38 h</td>
</tr>
</tbody>
</table>

**Level (U/mL)**

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>139.29 (134.06)</td>
<td>0.59</td>
</tr>
<tr>
<td>87.39 (80.69)</td>
<td>0.64</td>
</tr>
<tr>
<td>162.59 (133.04)</td>
<td>0.63</td>
</tr>
<tr>
<td>169.00 (136.33)</td>
<td>0.59</td>
</tr>
<tr>
<td>153.89 (137.28)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

*Notes.* Descriptives were based on 6,121 samples from 1,281 days and 165 caregivers.
Table 6

Associations between salivary alpha-amylase levels, daily experiences, and caregiving characteristics

<table>
<thead>
<tr>
<th></th>
<th>Waking</th>
<th>30-min after Waking</th>
<th>Before Lunch</th>
<th>Late Afternoon</th>
<th>Before Bed</th>
<th>AUCg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
</tr>
<tr>
<td>Intercept</td>
<td>144.66 (9.35)**</td>
<td>88.80 (5.61)***</td>
<td>164.13 (9.34)***</td>
<td>168.42 (9.54)***</td>
<td>155.88 (9.15)***</td>
<td>147.10 (7.64)***</td>
</tr>
<tr>
<td><strong>Within-person covariate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily ADS use</td>
<td>-7.55 (5.56)</td>
<td>-5.64 (3.04)</td>
<td>-1.09 (5.12)</td>
<td>-6.37 (5.56)</td>
<td>-4.20 (6.09)</td>
<td>-4.03 (3.19)</td>
</tr>
<tr>
<td>Daily non-care stressors</td>
<td>0.92 (2.81)</td>
<td>-1.90 (1.55)</td>
<td>2.41 (2.57)</td>
<td>-1.49 (2.84)</td>
<td>2.63 (3.09)</td>
<td>-0.29 (1.61)</td>
</tr>
<tr>
<td>Daily care-related stressors</td>
<td>1.31 (0.76)</td>
<td>0.53 (0.42)</td>
<td>-0.39 (0.70)</td>
<td>-1.95 (0.77)*</td>
<td>0.20 (0.84)</td>
<td>-0.35 (0.44)</td>
</tr>
<tr>
<td>Daily positive experience</td>
<td>-3.26 (2.73)</td>
<td>-1.02 (1.49)</td>
<td>3.00 (2.50)</td>
<td>-1.59 (2.72)</td>
<td>-1.51 (2.97)</td>
<td>-0.27 (1.58)</td>
</tr>
<tr>
<td>Daily sleep quality</td>
<td>4.58 (3.45)</td>
<td>1.05 (1.89)</td>
<td>-6.54 (3.13)*</td>
<td>1.87 (3.41)</td>
<td>-4.47 (3.73)</td>
<td>-1.58 (2.01)</td>
</tr>
<tr>
<td><strong>Between-person covariate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ADS days</td>
<td>9.38 (6.35)</td>
<td>8.73 (3.85)*</td>
<td>16.65 (6.41)**</td>
<td>10.21 (6.50)</td>
<td>12.20 (6.12)*</td>
<td>12.69 (5.38)*</td>
</tr>
<tr>
<td>Caregiver age</td>
<td>0.70 (0.88)</td>
<td>0.82 (0.54)</td>
<td>0.03 (0.89)</td>
<td>0.11 (0.90)</td>
<td>0.44 (0.85)</td>
<td>0.43 (0.75)</td>
</tr>
<tr>
<td>Caregiver gender</td>
<td>22.57 (26.69)</td>
<td>3.23 (16.21)</td>
<td>-3.82 (26.99)</td>
<td>21.00 (27.35)</td>
<td>19.13 (25.76)</td>
<td>9.44 (22.58)</td>
</tr>
<tr>
<td>Duration of care</td>
<td>-0.15 (0.20)</td>
<td>-0.15 (0.12)</td>
<td>0.08 (0.20)</td>
<td>-0.04 (0.20)</td>
<td>0.04 (0.19)</td>
<td>0.05 (0.16)</td>
</tr>
<tr>
<td>IWD's ADL dependency</td>
<td>-1.21 (18.77)</td>
<td>5.58 (11.38)</td>
<td>5.69 (18.93)</td>
<td>9.26 (19.18)</td>
<td>13.11 (18.07)</td>
<td>6.66 (15.93)</td>
</tr>
<tr>
<td>Average non-care stressors</td>
<td>-3.30 (7.26)</td>
<td>-6.43 (4.38)</td>
<td>-4.59 (7.30)</td>
<td>-7.24 (7.42)</td>
<td>-8.17 (7.07)</td>
<td>-6.93 (6.06)</td>
</tr>
<tr>
<td>Average care-related</td>
<td>0.06 (1.20)</td>
<td>0.80 (0.72)</td>
<td>-0.90 (1.20)</td>
<td>-1.60 (1.22)</td>
<td>0.48 (1.16)</td>
<td>-0.31 (1.01)</td>
</tr>
<tr>
<td>Average positive</td>
<td>4.40 (7.11)</td>
<td>3.43 (4.30)</td>
<td>-4.84 (7.16)</td>
<td>-8.37 (7.27)</td>
<td>3.28 (6.87)</td>
<td>-1.10 (5.96)</td>
</tr>
<tr>
<td>Average sleep quality</td>
<td>0.20 (8.78)</td>
<td>-4.42 (5.30)</td>
<td>-12.95 (8.82)</td>
<td>-9.69 (8.96)</td>
<td>-7.23 (8.49)</td>
<td>-8.96 (7.36)</td>
</tr>
</tbody>
</table>

Notes. All daily (within-person) covariates were person-mean centered. All between-person covariates were grand-mean centered. ADS = Adult day services. AUCg = Area under the curve with respect to ground, calculated using all 5 daily samples. For days missing AUCg, samples #1, 2, and 5 were used to calculate AUCg (n = 72). The total number of days for AUCg in the model was N = 1019. *p ≤ .05, **p ≤ .01, ***p ≤ .001.
Table 7

**Effect of ADS use on diurnal salivary alpha-amylase slopes covarying for daily experiences and caregiving characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
<td>Estimate (s.e.)</td>
</tr>
<tr>
<td>Intercept</td>
<td>140.26 (8.38)***</td>
<td>144.59 (8.95)***</td>
<td>104.07 (26.27)***</td>
<td>143.79 (8.70)***</td>
</tr>
<tr>
<td>S1</td>
<td>-109.56 (11.84)***</td>
<td>-112.06 (13.86)***</td>
<td>-95.43 (37.16)*</td>
<td>-107.79 (12.24)***</td>
</tr>
<tr>
<td>S2</td>
<td>14.86 (1.32)***</td>
<td>13.81 (1.53)***</td>
<td>6.55 (4.07)</td>
<td>14.36 (1.32)***</td>
</tr>
<tr>
<td>S3</td>
<td>0.91 (1.31)</td>
<td>2.47 (1.68)</td>
<td>10.25 (4.03)*</td>
<td>0.57 (1.35)</td>
</tr>
<tr>
<td>S4</td>
<td>-1.51 (0.48)***</td>
<td>-1.71 (0.58)**</td>
<td>-2.95 (1.50)*</td>
<td>-1.30 (0.48)**</td>
</tr>
<tr>
<td><strong>Within-person covariate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily ADS use</td>
<td>-</td>
<td>-9.78 (4.98)*</td>
<td>-5.66 (2.65)*</td>
<td>-5.55 (2.67)*</td>
</tr>
<tr>
<td>S1*daily ADS use</td>
<td>-</td>
<td>6.51 (13.37)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S2*daily ADS use</td>
<td>-</td>
<td>1.94 (1.48)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S3*daily ADS use</td>
<td>-</td>
<td>-2.86 (1.99)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S4*daily ADS use</td>
<td>-</td>
<td>0.37 (0.61)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Daily care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.05 (0.68)</td>
</tr>
<tr>
<td>S1*Daily care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.93 (1.68)</td>
</tr>
<tr>
<td>S2*Daily care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.36 (0.18)*</td>
</tr>
<tr>
<td>S3*Daily care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.33 (0.24)</td>
</tr>
<tr>
<td>S4*Daily care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.17 (0.08)*</td>
</tr>
<tr>
<td><strong>Between-person covariate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ADS days</td>
<td>-</td>
<td>-</td>
<td>9.24 (5.99)</td>
<td>8.26 (6.16)</td>
</tr>
<tr>
<td>S1*total ADS days</td>
<td>-</td>
<td>-</td>
<td>-3.21 (8.45)</td>
<td>-1.44 (8.66)</td>
</tr>
<tr>
<td>S2*total ADS days</td>
<td>-</td>
<td>-</td>
<td>1.99 (0.92)*</td>
<td>2.28 (0.94)*</td>
</tr>
<tr>
<td>S3*total ADS days</td>
<td>-</td>
<td>-</td>
<td>-2.22 (0.91)*</td>
<td>-2.10 (0.94)*</td>
</tr>
<tr>
<td>S4*total ADS days</td>
<td>-</td>
<td>-</td>
<td>0.34 (0.34)</td>
<td>0.16 (0.34)</td>
</tr>
<tr>
<td>Average care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.03 (1.12)</td>
</tr>
<tr>
<td>S1*Average care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.95 (1.60)</td>
</tr>
<tr>
<td>S2*Average care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.31 (0.17)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>S3*Average care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.18 (0.18)</td>
</tr>
<tr>
<td>S4*Average care-related stressors</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.17 (0.06)**</td>
</tr>
<tr>
<td>Average positive experience</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.37 (6.65)</td>
</tr>
<tr>
<td>S1*Average positive experience</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-7.71 (9.38)</td>
</tr>
<tr>
<td>S2*Average positive experience</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-1.53 (1.02)</td>
</tr>
<tr>
<td>S3*Average positive experience</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.71 (1.03)</td>
</tr>
<tr>
<td>S4*Average positive experience</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.04 (0.36)**</td>
</tr>
</tbody>
</table>

**Notes.** All daily (within-person) covariates were person-mean centered. All between-person covariates were grand-mean centered.

S1 = linear slope from waking to 30min post waking, S2 = linear slope from 30min post waking to before lunch, S3 = linear slope from before lunch to late afternoon, S4 = linear slope from late afternoon to before bed. n.s. within- and between-person effects were trimmed from Model 4.

Model 1 = Unconditional linear spline model, Model 2 = Within-person (daily) ADS effect model, Model 3 = Between-person (total) ADS days effect model, Model 4 = Within- and between- person ADS effects model with covariates.

The trimmed within-person effects were: daily non-care stressors, daily positive experience, and daily sleep quality.

The trimmed between-person effects were: age, gender, duration of care, ADL dependency, average non-care stressors, average sleep quality.

*p ≤ .05, **p ≤ .01, ***p ≤ .001.
Figure 3.

*The typical diurnal alpha-amylase trajectory among dementia family caregivers*

**Notes.** Salivary alpha-amylase (sAA) levels were measured in um/l.
AD, AR1–AR3 are the four linear components specified in the model.
AD is the first linear decline slope from wake-up to 30min after wake-up.
AR1 is the first linear rise from 30min after wake-up to before lunch.
AR2 is the second linear rise from before lunch to late afternoon.
AR3 is the third linear rise from late afternoon to before bed.
The association between total ADS days and alpha-amylase diurnal slopes

Notes. Salivary alpha-amylase (sAA) levels were measured in um/l. sAA trajectories were based on parameter estimates in Model 3, the between-person (total) ADS days effect model as presented in Table 3. Greater ADS use was defined as one standard deviation (SD) above the average ADS days. Lower ADS use was defined as one standard deviation (SD) below the average ADS days.
CHAPTER 4. STUDY 3.

Linking Daily HPA and SNS Activity to Family Caregiver Health over Time:
Caregiving Transitions and Adult Day Services Use

4.1 Background and Literature Review

As Selye (1976) p. 427 put it almost four decades ago: “It is only by the intensity of its manifestations – the adrenal enlargement, the increased corticoid concentration in the blood, the loss of weight, and so forth – that we can recognize the presence and gauge the intensity of stress.” Biological mechanism is one way of stress manifestation, which can be reliably detected and measured. Such processes may be the underlying mechanism between stressor exposures and long-term health and well-being.

**Hypothalamic-pituitary-adrenal axis functioning and stress**

The major part of the neuroendocrine systems that is closely associated with stress functioning is the hypothalamic-pituitary-adrenal (HPA) axis, which regulates many important bodily processes in response to stress, including metabolism, digestion, immune system, cognition, mood and emotions. The HPA axis is one potential biological mechanism for chronic stress to get under the skin (Miller et al., 2007). Because of the central role HPA plays in reaction to stress and its sensitivity to both psychosocial and physical stressors, its neuroendocrine functioning and hormone products have attracted particular research attention. Briefly, when the brain detects a stimulus, the neurons in the paraventricular nucleus of the hypothalamus produces corticotrophin-releasing hormone (CRH). CRH gets through the hypophyseal portal circulation to the anterior pituitary gland, which responds by releasing a pulse of adrenocorticotropin hormone (ACTH), as well as arginine vasopressin (AVP), which is central to the fight-or-flight response (Dickerson & Kemeny, 2004; Piazza et al., 2010). Then
ACTH gets through the peripheral circulation to the adrenal glands, which produce cortisol in a tissue layer of zona fasciculata (Sapolsky et al., 1986). The primary hormone/mediators of the HPA axis are CRH, ACTH, AVP, dehydroepiandrosterone (DHEA) and its sulfated form DHEA-s, and cortisol. DHEA(-s) is similar to cortisol, because it is probably coreleased with cortisol in response to ACTH signaling. However, DHEA(-S) is anabolic, while cortisol is a catabolic hormone (Epel, 2009). Anabolic hormones such as androgens (i.e., DHEA(-S)) are important for stress and aging; they decrease with age, and they are often associated with poor metabolic health. DHEA(-S) often functions as an antiglucocorticoid and has buffering effects on inflammation and oxidative stress. DHEA(-S) can prevent oxidative stress damage in neurons, and it can block cortisol-mediated excitatory neurotoxicity. 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 (Epel, 2009).

As the end product of this cascade, cortisol has been the center of research because of its regulatory functions and relatively easy access to measurement. Cortisol activity is responsive to both acute and chronic stressors (Miller et al., 2007). In addition, cortisol is the hypothesized biological mechanism for stress to bring about mal-function and disease in the body. Such models have been applied to psychiatric disorders of depression, medical conditions of cancer and diabetes, and lifestyle problems such as obesity and fatigue. Chronic stressors can both increase or decrease cortisol output. Many of these findings articulate that stressor triggers disease by increasing cortisol output (hypercortisolism), exposing tissues to its elevated concentrations. However, cortisol deficiency (hypocortisolism) has also been related to disease pathogenesis such as posttraumatic stress disorder, rheumatoid arthritis, and chronic fatigue.
Thus, stress-induced increases and decreases in cortisol output can be both detrimental in a similar way.

**Salivary alpha-amylase as an indicator of stress**

Salivary alpha-amylase (sAA) can serve as a non-invasive physiological marker for psychological stressors. A growing body of research suggests that stressors activate the sympathetic nervous system (SNS), and sAA can be a sensitive and reliable marker of the experienced stress (Granger, Kivlighan, El-Sheikh, Gordis, & Stroud, 2007; Piazza et al., 2010). sAA release is elicited by the SNS activation, which controls the salivary glands. sAA parallels norepinephrine increases in response to stressor 5-10 minutes after norepinephrine releases, and is hypothesized to be a useful biomarker of the SNS activation.

sAA has the following basic properties and functions. As an enzyme, sAA is unique from other salivary biomarkers such as androgens (i.e., DHEA(-s)) or glucocorticoids (i.e., cortisol) in that it is not transported actively or diffused passively into saliva from the general circulation. sAA is produced in the oral cavity by three major salivary glands: the parotid, submandibular, and sublingual glands. A number of other minor glands also contribute to salivary outflow. The salivary glands are part of the digestive tract, and a primary biological function of α-amylase is to digest carbohydrates and starch. Other secondary functions of α-amylase are to clear bacteria from the mouth and to prevent bacteria attaching to oral surfaces, and lower α-amylase activity is associated with oral disease. sAA is not present in newborn infants, starts to show a steep rise which parallels the timing of solid foods introduction, and reaches maximum levels by about 6 years of age.

**Stress response as a multidimensional construct**
Since stress is known to activate the two major biological systems, the HPA axis and the SNS, there is an emerging trend to incorporate multiple biomarkers of salivary cortisol, DHEA-s, and sAA of the HPA and SNS activities. These studies, nevertheless, have employed different methods to operationalize such synchrony of biomarkers in response to stressors. Relying on cross-correlation analysis with time series, Engert and colleagues (2011) found that preceding sAA was significantly correlated with salivary cortisol levels at a later time and the lag was about 14 minutes in a laboratory stress task. Using regression analyses, Vigil and colleagues (2010) observed flattened baseline cortisol levels and elevated sAA levels among a sample of hurricane Katrina victims. In another study, Ali and Pruessner (2012) compared different measures of the relationship between HPA and SNS using the ratio of sAA over cortisol, the ratio of cortisol over sAA, or either biomarker alone. They further associated these biomarkers with subjective appraisals of chronic stress and depression.

One primary purpose of these studies was to examine distinctive biological effects of stressors and associations with health and diseases (Ghiciuc et al., 2011). With regard to cortisol, there is strong evidence showing that changes in laboratory-induced cortisol as well as basal levels were associated with disease processes or risks for diseases such as asthma (Wolf, Nicholls, & Chen, 2008). Granger and colleagues (2006) found that greater sAA in response to acute laboratory-induced stressors were observed in children who also had more parent-reported health problems and illnesses. HPA and SNS activities in response to the chronic stress of caregiving may have similar health implications among family caregivers of IWDs.

**Biomarker as the pre-disease pathways**

The concept of pre-disease pathways describes the biological influences and associations with behavioral, psychological, and social influences that extend before the onset of diseases and
mortality (Singer & Ryff, 2001). To evaluate these precursors to morbidity onset at distant time points, and to study a multitude of them simultaneously are important tenets guiding empirical research on health. A more distant time point to disease onset is necessary to facilitate understanding about links between early antecedents and later risk factors, as well as the etiological processes leading to disease outcomes.

Further, based on the theme of integrative research, risk and protective factors across multiple systems need to be assessed simultaneously. Chronic under-exposure to protective factors and repeated exposure to challenges can disrupt biological regulations central to physiological homeostasis and health. Optimal operationalization of such risk across bodily systems over time will have implications on characterization of pre-disease pathways. Thus there is the need to identify early biomarkers of pre-disease states, to identify behavioral risks and protective factors that exacerbate or ameliorate pre-disease pathways, and to examine an array of biological precursors to disease simultaneously. Daily biomarkers can serve as a precise summary of individuals’ biological response to the mosaic of daily experiences. Linking the daily biomarkers to long-term measures of health approximates the construct of pre-disease pathway, which helps quantify the health implications of daily and chronic stressors.

**Caregiver health and caregiving transition**

Transition often means institutionalization and bereavement in the caregiving literature. Both transitions involve the removal of caregiving responsibilities, but we focused in this study only on institutionalization. Placing the care recipient in a nursing home or similar institutions happens when the care recipient still needs active care, which is sometimes provided partly by the caregiver (Gaugler et al., 2000). Placement may also be associated with health in varying ways. Studies have found that placement may be precipitating by caregivers’ worsening health
Furthermore, guilt and concern about quality of care may also contribute to caregivers’ ongoing feelings of distress. On the other hand, getting relief from the demands of daily care may have a restorative effect on health and functioning (Gaugler et al., 2003). Thus, we believed it was important to examine the possible associations of placement with biomarkers and health. Additionally, although placement into a nursing home or similar institutional setting is the most common type of transition, caregivers may turn care over to other family members. Although this transition is much less common than placement, we considered its association with health outcomes. We did not include the transition to bereavement, however, because bereavement would not be precipitated by caregivers’ declining health and there is little evidence that health worsens after bereavement (Schulz, Beach, Lind, & et al., 2001).

A number of prior studies have noted the association between caregiver health problems and placement of the care recipient. Baumgarten and colleagues (1994) reported that, compared with caregivers who did not have any transitions, the ones who institutionalized their relatives showed downward health trajectories. Gaugler and colleagues (2003) found that caregivers who self-rated their health as poor institutionalized the IWDs sooner. A study by McCann and colleagues (2004) showed that caregiver health predicted beginning and continuing in the caregiving role. Buhr, Kuchibhatla, & Clipp (2006) studied the reasons for nursing home placement based on a 3-year longitudinal study. Among caregivers who institutionalized their IWDs, nearly half of them indicated their own health problems as the primary reason.

**ADS use and the ‘Health Preserving’ hypothesis**

Interventions that lower caregivers’ stressor exposures may reduce the risk of having poor health, particularly for caregivers of IWDs who often provide extensive help and ongoing
supervision. Community-based long-term care services such as ADS programs provide a predictable amount of time away from IWDs, reducing exposure to care-related stressors and creating opportunities for caregivers to engage in self-care activities (Zarit et al., 2011). Regular ADS use was effective in lowering depressive symptoms and anger (Zarit, Kim, Femia, Almeida, & Klein, 2014; Zarit, Stephens, Townsend, & Greene, 1998); other studies have also found that as a result of ADS use, caregivers report better self-efficacy in behavior management and enhanced general well-being, which in turn enables them to provide more efficient home care (Gitlin, Reever, Dennis, Mathieu, & Hauck, 2006). Additionally, ADS use was found to 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 (Klein et al., 2014); on days following ADS use, DHEA-s levels were also higher (Zarit, Whetzel, et al., 2014).

Based on the positive effects of ADS found in prior studies on caregiver health and well-being, the current study hypothesizes that more frequent and sustained ADS use may have positive associations with some dimensions of caregiver health and well-being over time.

4.2 The Current Study

The current study takes a multidimensional approach to examine the association between daily stress biomarkers and health change over a one-year period (Liu, Kim, & Zarit, 2015). It extends the previous research in the following ways. First, unlike much of the existing literature that focused on a single measure of health, the current study examined changes in both functional limitation and bodily pain. The reason to include them as outcomes was that a prior study on this sample showed that caregivers had increasing functional limitations and decreasing bodily pain over a one year period (Liu et al., 2015). Second, this study was among the first studies to
explore the health implications of daily stress biomarkers of both HPA and SNS systems. As there is a lack of consensus on the best way to operationalize pre-disease pathways, we summarized daily biomarkers using daily total output based on the existing formula for salivary cortisol, DHEA-S and sAA (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Third, we examined the effects of ADS use and caregiving transitions during the course of study on the association between daily biomarkers and health change. To examine the effect of total ADS days per week on caregivers who had transitions versus who did not, we considered the interaction between caregiving transitions and ADS use on health change. Figure 5 presents a conceptual model of the current study.

The current study was guided by the stress process model (Pearlin et al., 1990), and built upon previous studies on biomarkers, chronic stress, and health. Health change over time was related to daily stress biomarkers, ADS use, caregiving characteristics at baseline, as well as caregiving transition during the study period. The study makes specific hypotheses on the associations between daily biomarkers and physical health over time for cortisol, DHEA-S, and sAA as the following.

**Hypothesis 1:** Lower average daily total output of all three biomarkers will be associated with worsening health over time among caregivers who experienced a transition.

**Hypothesis 2:** the extent of ADS use will influence the association between caregiving transitions, daily total output of all three biomarkers and health trajectory in the 12-month period. Specifically, among caregivers who had a transition, and who used fewer ADS days at baseline, lower daily total output of biomarkers will be associated with worsening health over time.

4.3 Methods

**Participants and procedures**
Participants were 165 family caregivers who were a) providing primary care to IWDs that lived in the same household, b) reporting the IWD having a type of dementia such as Alzheimer’s disease that was diagnosed by a physician, c) using ADS programs at least two days a week, d) participating in an 8-day diary study and having provided five saliva samples each day as part of the Daily Stress and Health (DaSH) study (Zarit, Kim, et al., 2014). Table 1 presents demographic characteristics of caregivers and the IWD they were caring for. In total, the 165 caregivers had 6,132 valid cortisol samples, 6,121 valid sAA samples, and 6,003 valid DHEA-s samples. A sample was invalid if: 1) the participant was awake for less than 12hr or greater than 20hr \( (n = 14) \), or 2) the participant woke up after 12pm \( (n = 0) \), or 3) there was a greater than 10nmol 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 \( (n = 99) \).

Recruitment was conducted at ADS programs in Northern and Central New Jersey, the Philadelphia and Pittsburgh metropolitan areas, Northern Virginia, and Denver, Colorado. Programs provided fliers to potential participants, and posted announcements in newsletters. 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 shipment back to the lab. Daily interviews were conducted in the evenings of
the 8 days by a telephone interviewer from the Penn State Survey Research Center. In the
interviews, participants reported daily stressors and affect and confirmed times of the saliva
samples. 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 α-amylase 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 α-amylase, and 10% for DHEA-s were
subject to repeat testing. Values used in data analyses are the averages of duplicate tests.

Measures

**Physical health.** We took a multidimensional approach to health, using two scales
derived from the Medical Outcomes Studies (MOS) 36-item short form health survey (SF-36)
(Ware & Sherbourne, 1992) that addressed functional health and global subjective health. We
did not include items which assessed emotional health and well-being as they are included in
other study measures. The measure has been widely used in medical outcome studies with
younger and older adults and has good subscale reliabilities and validity (Hays & Stewart, 1992;
Stewart, Ron, & Ware, 1988). The two scales were:

*Functional limitation.* This subscale (9-item, $\alpha = .82$) 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 (Stewart
Caregivers were asked about how much physical limitation (3-point scale; coded 1 = *not limited* to 3 = *limited a lot*) they had in carrying out these activities, and higher scores indicated greater functional limitation.

*Bodily pain.* The single-item subscale asked caregivers how much bodily pain have they generally had during the past month (6-point scale; coded 1 = *none* to 6 = *very severe*). Higher scores indicated more severe sensation of bodily pain.

**Key predictors and covariates.**

*Caregiving transition.* Caregiving transition (1 = *had a transition* and 0 = *did not have a transition*) was coded to indicate any types of transition reported at either 6- or 12-month interview, such that the caregiver was no longer the primary caregiver of their living IWDs. Not having a transition indicated that the caregiver was still providing the primary care.

*ADS use.* ADS use at the between-person level was coded as total number of ADS days per week at baseline (\(M = 3.89\) days, \(SD = 1.15\) days).

*Daily biomarkers.* The sample test volume for salivary cortisol was 25 ul. The assay had a lower limit of sensitivity of 0.03 μg/dl, with an average inter- and intra-assay covariance of less than 7% and 4%, respectively. Cortisol measurement units were converted to nmol/ml (μg/dl × 27.6). The sample test volume for salivary DHEA-S was 50 ul. 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/mL (i.e., ng/mL × 2.71). The sample test volume for sAA was 10 ul. Measurement units were expressed in nmol/ml (ng/mL × 2.71). Original values without transformations were used for the analysis. Daily total outputs for all three biomarkers were measured as area under the
curve with respect to ground (AUCg) using five daily values based on existing formula (Pruessner et al., 2003). Two types of daily biomarkers were used as predictors of caregivers’ longitudinal health trajectories for each of the three biomarkers. The average daily total output was calculated as the mean level across the daily observation period at baseline; the difference in average daily total output on ADS versus non-ADS days was also calculated to test any within-person intervention response.

**Covariates.** We considered additional variables from the baseline interview that are often associated with caregiver physical health as covariates: caregiver age, relation type (1 = *spouse* and 0 = *other kin relationship*), depressive symptoms (depression subscale from the Non-Specific Psychological Distress Scale; 7 items on a 5-point scale ranging from 1 = *none of the day* to 5 = *all day*; coded so that higher scores indicated more depressive symptoms; $\alpha = .81$; Kessler et al., 2002), caregiving role overload (3 items on a 4-point scale ranging from 1 = *none of the time* to 4 = *all of the time*; coded so that higher scores indicated more subjective experiences of being worn out and overloaded; $\alpha = .63$) (Pearlin et al., 1990), and caregiving role captivity (3 items on a 4-point scale ranging from 1 = *none of the time* to 4 = *all of the time*; coded so that higher scores indicated that the caregiving role was unwanted; $\alpha = .83$) (Aneshensel et al., 1995; Pearlin et al., 1990).

**Analysis plan**

The average daily total output was used to test the first hypothesis on average association between biomarkers and longitudinal health change, in the context of caregiving transitions (Model 1). To test the third hypothesis on extent of ADS use, total ADS days per week was added into Model 1 to predict health trajectories (Model 2). The hypotheses were tested using
three growth curve models for each of the three biomarkers, using both functional limitation and bodily pain over time as outcomes. The level 1 equation in all three models was specified as:

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

(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 average daily total output \((Model 1)\), and the extent of baseline ADS use \((Model 2)\) on caregiver health trajectories in the context of caregiving transitions, while controlling for caregiver characteristics. Level 2 equations in Model 1 were specified as:

\[ \pi_{0i} = \beta_{00} + \beta_{01} (\text{Caregiver age}_i) + \beta_{02} (\text{Spouse caregiver}_i) + \beta_{03} (\text{Role overload}_i) + \beta_{04} (\text{Role captivity}_i) + \beta_{05} (\text{Depressive symptoms}_i) + \beta_{06} (\text{Average daily total output}_i) + \beta_{07} (\text{Caregiving transition}_i) + \nu_{0i} \] 

\[ \pi_{1i} = \beta_{10} + \beta_{11} (\text{Average daily total output}_i) + \beta_{12} (\text{Caregiving transition}_i) + \beta_{13} (\text{Average daily total output}_i) \times (\text{Caregiving transition}_i) \] 

(2)

where \(\beta\)s are population-level parameters; the person-specific intercept, \(\pi_{0i}\), from equation (1) is now modeled as functions of average daily total output of cortisol, DHEA-S, and sAA at baseline and caregiving transition, while controlling for other caregiving characteristics; the person-specific linear time slope, \(\pi_{1i}\), is also modeled as functions of average daily total output of cortisol, DHEA-S, and sAA at baseline, caregiving transition, and the interaction between these two terms. \(\nu_{0i}\) is between-person differences in the intercept with a variance, \(\sigma_{0}^2\).

Next, to test the effect of extent of baseline ADS use on the association between biomarkers and health change in the caregiving transition context, total ADS days per week at baseline were used to predict health trajectories. Level 2 equations in Model 2 were specified as:

\[ \pi_{0i} = \beta_{00} + \beta_{01} (\text{Caregiver age}_i) + \beta_{02} (\text{Spouse caregiver}_i) + \beta_{03} (\text{Role overload}_i) + \beta_{04} (\text{Role captivity}_i) + \beta_{05} (\text{Depressive symptoms}_i) + \beta_{06} (\text{Average daily total output}_i) + \] 

(4)
\[ \beta_{07}(\text{Caregiving transition}_i) + \beta_{08}(\text{Total ADS days}_i) + \nu_{0i} \]

\[ \pi_{1i} = \beta_{10} + \beta_{11}(\text{Average daily total output}_i) + \beta_{12}(\text{Caregiving transition}_i) + \beta_{13}(\text{Total ADS days}_i) + \beta_{14}(\text{Average daily total output}_i) \times (\text{Caregiving transition}_i) + \beta_{15}(\text{Average daily total output}_i) \times (\text{Total ADS days}_i) + \beta_{16}(\text{Caregiving transition}_i) \times (\text{Total ADS days}_i) \]

where the person-specific linear time slope, \( \pi_{1i} \), is now modeled as functions of total ADS days at baseline, average daily total output of cortisol, DHEA-S, and sAA at baseline, caregiving transition, and the interactions between these three terms. \( \nu_{0i} \) is between-person differences in the intercept with a variance, \( \sigma^2_\nu \). All models were fit to both repeatedly-measured health outcomes, and all between-person covariates on demographics and caregiving characteristics were grand-mean centered.

### 4.4 Results

Descriptives on caregiver characteristics were run as a preliminary analysis, which are presented in Table 8. Next, to test the first hypothesis, we fit Model 1 using average daily total output and caregiving transitions as key predictor in the level-2 equations. Functional limitation trajectory in the 12-month period was associated with the daily total outputs of all three biomarkers, in the context of caregiving transitions. First, caregiving transition moderated the effect on the association between functional trajectory and daily total output of cortisol (\( \beta = -0.007, p < .0001, \text{Model 1.1} \)), DHEA-S (\( \beta = 0.0015, p = .02, \text{Model 1.2} \)), and sAA (\( \beta = -0.0001, p = .0002, \text{Model 1.3} \)), as indicated by three significant 3-way interactions in the models. Specifically, among caregivers who experienced a transition, lower cortisol daily total output (Figure 6), greater DHEAs daily total output (Figure 7), and lower sAA daily total output (Figure
8) was associated with increasing functional limitations over time. We did not find any significant association for bodily pain over time. These models are presented in Table 9.

Next, we fit Model 2 to test the hypothesis on the extent of ADS use at baseline. The model showed that the associations between functional limitation trajectory and daily total outputs of cortisol and sAA in the context of caregiving transitions were further modified by the extent of ADS use. First, the significant 4-way interaction in Model 2.1 ($\beta = 0.004$, $p = .013$) showed that caregiving transition 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, lower daily cortisol total output was associated with increasing functional limitations (Figure 9). Caregivers who experienced a transition but used greater than average ADS days per week did not show such patterns of association (Figure 9). Second, the significant 4-way interaction in Model 2.2 ($\beta = 0.0001$, $p = .002$) showed that caregiving transition 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 10). Caregivers who experienced a transition but used greater than average ADS days per week did not show such patterns of association (Figure 10). We did not find any association for DHEA-S or changes in bodily pain over time. All the significant findings from Models 2 are presented in Tables 10. All models controlled for the same sets of covariates.

4.5 Discussion
This study is among the first to explore associations between daily biomarkers and long-term health among family caregivers of IWDs. Some of its strengths included the longitudinal measures on multiple dimensions of health, baseline biomarkers measured across days such that within-person variance was minimized, and the considerations of an intervention effect in the caregiving transition context. It contributes to the literature on an important but largely unanswered “so what” question on stress biomarkers and their health implications.

**Biomarkers and health in the caregiving transition context**

The findings showed that the health trajectories, specifically how functional limitations change over time, were associated with daily stress biomarkers of both HPA and SNS in the caregiving transition context. The findings on lower cortisol and sAA daily total outputs were consistent with previous studies on the allostatic load (AL) model of chronic stress and health problems (Juster et al., 2010). Prolonged secretion of the stress hormone such as cortisol can be detrimental, causing dysregulation in the brain and body. Hypocortisolism and lower sympathetic activity may imply a potential mechanism for increased susceptibility to functional declines (Miller et al., 2007; Wolf et al., 2008). The association between hypocortisolism, lower sAA levels, and increasing functional limitation was only present among caregivers with transitions confirmed that physical health is an important resource for caregiving roles (Buhr et al., 2006).

The finding on associations between greater DHEA-S levels and increasing functional limitations among caregivers who had transitions is a bit puzzling. As an antagonist to cortisol, existing research generally suggests that lower DHEA-S levels were associated with greater health risks (Juster et al., 2010). Chronically stressed populations such as caregivers of IWDs
typically have reduced DHEA-S levels than non-stressed controls (Moriguchi Jeckel et al., 2010), but prior studies suggested gender could be a contextual factor (Kudielka et al., 1998). The fact that our sample consisted primarily of women caregivers may have contributed to the contradictory findings. More longitudinal studies are needed to further explore the associations between DHEA-S, chronic stress and health.

**ADS use, caregiver health, and caregiving transitions**

The findings on ADS use extend the literature on its psychological and physical benefits for caregivers of IWDs (Liu et al., 2015; Zarit, Kim, et al., 2014). There was an interesting finding on the extent of baseline ADS use on the biomarker-health association in the caregiving transition context. Among caregivers who placed relatives, the ones who had fewer ADS days per week seemed to show an association between low cortisol levels and increasing functional impairment over time. Such association was not present among caregivers who placed relatives but had more days of ADS use. The same patterns of finding also apply to daily sAA total output. The significant 4-way interaction between biomarkers, health change, total ADS days, and caregiving transition confirms prior findings on the health benefits of ADS use (Liu et al., 2015). Similar to a medical drug, there appeared to be a dosage effect, and more than average ADS days per week (average = 3.86 days) seemed to bring greater physical benefits to decrease functional impairment. This finding is consistent with the literature on health benefits of caregiving respite, because of reduced care-related stressor exposures (Zarit et al., 2011).

**Limitations**

The study has some limitations. First, although there were two health outcome measures, there were only three measurement occasions followed up over 12 months. More health
dimensions measured over a longer time span 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, our sample of family caregivers 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, which consisted of primarily women caregivers. Caregivers are a dynamic group, and caregiving can be more beneficial than detrimental to caregiver health (Freedman, Cornman, & Carr, 2014). Thus it is difficult to generalize the current findings to other populations of caregivers, in spite of the interesting insights on biomarkers and health association.

The findings have implications for ways to support informal caregivers through public policies. Family caregivers lay the foundation of the nation’s long-term care system, who contributed an important component of economy to the society (Gibson & Houser, 2007; Reinhard, Feinberg, Choula, & Houser, 2015). The value of family caregiving, however, has been largely unrecognized in policy making about the costs of long-term services and supports. Empirical studies have shown that caregiving respite such as ADS use can provide a predictable amount of relief to caregivers by lowering primary stressor exposures. The benefits of community-based ADS programs on caregiver health and well-being are more realistic than hypothesized. How these programs may become part of the routine policy on caregiver support will have important implications for caregiver well-being, and the quality of the nation’s long-term services and supports system.
### 4.6 Tables and Figures

**Table 8**

*Caregivers’ Characteristics at Baseline (N = 165)*

<table>
<thead>
<tr>
<th></th>
<th>M or Freq</th>
<th>SD or %</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.99</td>
<td>10.70</td>
<td>39</td>
<td>89</td>
</tr>
<tr>
<td>Female</td>
<td>119</td>
<td>87.50</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Spouse</td>
<td>64</td>
<td>38.79</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Child</td>
<td>80</td>
<td>58.82</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Education&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.41</td>
<td>1.21</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Married with a partner</td>
<td>89</td>
<td>65.44</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Depressive symptoms&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.53</td>
<td>0.62</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Role overload&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.81</td>
<td>0.65</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Role captivity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.13</td>
<td>0.77</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Duration of care&lt;sup&gt;d&lt;/sup&gt;</td>
<td>64.42</td>
<td>46.76</td>
<td>3</td>
<td>216</td>
</tr>
<tr>
<td>Number of ADS days per week</td>
<td>3.86</td>
<td>1.17</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>IWD’s ADLs dependency&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.01</td>
<td>0.50</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

*Note.* ADS = adult day services; IWD = individual with dementia; ADL = activities of daily living.

<sup>a</sup>Measured on a 6-point scale: 1 (*less than high school*) to 6 (*post college degree*).

<sup>b</sup>Measured as the mean of 7 items on a 5-point scale: 1 (*none of the day*) to 5 (*all day*).

<sup>c</sup>Measured as the mean of 3 items on a 4-point scale: 1 (*none of the time*) to 4 (*all of the time*).

<sup>d</sup>Measured in months.

<sup>e</sup>Measured as the mean of 13 ADL items on a 4-point scale: 1 (*does not need help*) to 4 (*cannot do without help*).
Table 9

The association between health trajectories and daily biomarkers in the context of caregiving transitions

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Functional Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1.1</td>
</tr>
<tr>
<td></td>
<td>Cortisol AUCg</td>
</tr>
<tr>
<td>Interception</td>
<td>8.000 (0.244)***</td>
</tr>
<tr>
<td>Time</td>
<td>0.007 (0.015)</td>
</tr>
<tr>
<td>Caregiving transition</td>
<td>0.181 (0.658)</td>
</tr>
<tr>
<td>Average cortisol daily total output</td>
<td>-0.005 (0.005)</td>
</tr>
<tr>
<td>Average DHEA-S daily total output</td>
<td></td>
</tr>
<tr>
<td>Average sAA daily total output</td>
<td></td>
</tr>
<tr>
<td>Time × caregiving transition</td>
<td>0.009 (0.045)</td>
</tr>
<tr>
<td>Time × Average cortisol daily total output</td>
<td>0.000 (0.000)</td>
</tr>
<tr>
<td>Time × Average DHEAs daily total output</td>
<td></td>
</tr>
<tr>
<td>Time × Average sAA daily total output</td>
<td></td>
</tr>
<tr>
<td>Time × caregiving transition × Average cortisol daily total output</td>
<td>-0.007 (0.002)***</td>
</tr>
<tr>
<td>Time × caregiving transition × Average DHEA-S daily total output</td>
<td></td>
</tr>
<tr>
<td>Time × caregiving transition × Average sAA daily total output</td>
<td></td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
</tr>
<tr>
<td>Caregiver age</td>
<td>0.098 (0.028)***</td>
</tr>
<tr>
<td>Spouse caregiver</td>
<td>-0.811 (0.574)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>1.074 (0.383)**</td>
</tr>
<tr>
<td>Role overload</td>
<td>0.838 (0.341)*</td>
</tr>
<tr>
<td>Role captivity</td>
<td>-0.340 (0.299)</td>
</tr>
<tr>
<td>Random effects</td>
<td></td>
</tr>
<tr>
<td>Intercept VAR</td>
<td>4.795 (0.703)***</td>
</tr>
<tr>
<td>Residual VAR</td>
<td>1.245 (0.130)***</td>
</tr>
<tr>
<td>-2 Log likelihood</td>
<td>1284.6</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------</td>
</tr>
<tr>
<td>AIC, BIC</td>
<td>1288.6, 1294.3</td>
</tr>
</tbody>
</table>

**Notes.** All between-person covariates were grand-mean centered.

*p ≤ .05, **p ≤ .01, ***p ≤ .001.
### Table 10

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

<table>
<thead>
<tr>
<th>Fixed effects</th>
<th>Cortisol AUCg</th>
<th>sAA AUCg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed effects</strong></td>
<td>Model 3.1</td>
<td>Model 3.2</td>
</tr>
<tr>
<td>Intercept</td>
<td>7.999 (0.240)***</td>
<td>8.002 (0.248)***</td>
</tr>
<tr>
<td>Time</td>
<td>0.006 (0.014)</td>
<td>0.008 (0.015)</td>
</tr>
<tr>
<td>Caregiving transition</td>
<td>0.259 (0.650)</td>
<td>-0.014 (0.668)</td>
</tr>
<tr>
<td>Average cortisol daily total output</td>
<td>-0.006 (0.005)</td>
<td>0.000 (0.000)</td>
</tr>
<tr>
<td>Average sAA daily total output</td>
<td>0.000 (0.000)</td>
<td>0.000 (0.000)</td>
</tr>
<tr>
<td>Total ADS days</td>
<td>0.051 (0.193)</td>
<td>0.088 (0.202)</td>
</tr>
<tr>
<td>Time × caregiving transition</td>
<td>0.030 (0.044)</td>
<td>-0.010 (0.054)</td>
</tr>
<tr>
<td>Time × Average cortisol daily total output</td>
<td>0.000 (0.000)</td>
<td>0.000 (0.000)</td>
</tr>
<tr>
<td>Time × Average sAA daily total output</td>
<td>-0.017 (0.012)</td>
<td>-0.023 (0.012)</td>
</tr>
<tr>
<td>Time × Total ADS days</td>
<td>-0.005 (0.002)***</td>
<td></td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver age</td>
<td>0.099 (0.027)***</td>
<td>0.062 (0.028)*</td>
</tr>
<tr>
<td>Spouse caregiver</td>
<td>-0.853 (0.573)</td>
<td>-0.495 (0.586)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>0.979 (0.377)*</td>
<td>1.144 (0.395)**</td>
</tr>
<tr>
<td>Role overload</td>
<td>0.937 (0.335)**</td>
<td>0.661 (0.350)**</td>
</tr>
<tr>
<td>Role captivity</td>
<td>-0.364 (0.299)</td>
<td>-0.545 (0.309)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>Random effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept VAR</td>
<td>4.621 (0.679)***</td>
<td>4.917 (0.732)***</td>
</tr>
<tr>
<td>Residual VAR</td>
<td>1.158 (0.122)***</td>
<td>1.240 (0.132)***</td>
</tr>
<tr>
<td>-2 Log likelihood</td>
<td>1300.8</td>
<td>1344.9</td>
</tr>
<tr>
<td>AIC, BIC</td>
<td>1304.8, 1310.5</td>
<td>1348.9, 1354.6</td>
</tr>
</tbody>
</table>

*Notes.* All between-person covariates were grand-mean centered.
ADS = Adult day services.
*p ≤ .05, **p ≤ .01, ***p ≤ .001.*
Figure 5.

*Conceptual model of the study*
Figure 6.

*Changes in functional limitation and daily cortisol total output*
Figure 7.

*Changes in functional limitation and daily DHEAs total output*
Figure 8.

Changes in functional limitation and daily sAA total output
Figure 9.

*Changes in functional limitation and cortisol daily total output for caregivers who had lower versus higher than average ADS days per week*
Figure 10.

Changes in functional limitation and sAA daily total output for caregivers who had lower versus higher than average ADS days per week.
### 4.7 Appendix

Specific transition types at 6 months and 12 months

<table>
<thead>
<tr>
<th>Type of transition</th>
<th>n</th>
<th>6m</th>
<th>12m</th>
</tr>
</thead>
<tbody>
<tr>
<td>No transition @6m</td>
<td>147</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Transitioned at 6m</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sum of cases @ 6m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>Deceased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>NH/Assisted living</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Other types</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>With another family member</td>
<td></td>
</tr>
<tr>
<td>No transition at12m</td>
<td>119</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Transitioned at12m</td>
<td>25</td>
<td>Sum of new cases @ 12m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Deceased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>NH/Assisted living</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Other types</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>With another family member</td>
<td></td>
</tr>
</tbody>
</table>

**Notes.**

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

The analysis did not include cases whose relatives deceased at either 6 months or 12 months (n = 31).

NH = Nursing home.
Chapter 5. CONCLUSION

Together, the three studies depict a coherent picture on physiological implications of caregiving among older dementia caregivers in various daily contexts. The studies are among the first to examine multiple neuroendocrine biomarkers of stress in relation to an intervention, and in the context of daily experiences and caregiving transitions. The first study on cortisol regulation extends the literature by showing at a daily (within-person) level that stressor exposure may be associated with elevated cortisol levels at certain time of the day (i.e., before bed). Daily ADS use is associated with a more robust CAR, which boosts energy and may have the physiological benefits for caregivers who are chronically stressed.

Similarly, the second study on salivary alpha-amylase (sAA) regulation also utilizes a daily diary design over eight consecutive days. The consideration of ADS use makes it possible to examine sAA diurnal regulation across high- versus low-stress days. At the within-person level, greater daily care-related stressor exposures is associated with lower sAA levels in the late afternoon, and a blunted rise between 30 minutes after awakening and before lunch. At both the within- and between-person levels, more daily and average care-related stressors were related to a greater rise between late afternoon and before bed. These findings confirm the physiological toll of caregiving. The chronic stress of caregiving is likely to be associated with an attenuated sAA profile. ADS use, however, seems to have a restorative effect. Specifically, more ADS days are associated with higher sAA levels in three daily sampling occasions (e.g., 30 minutes after waking, before lunch, and before bed), and higher daily total output.

The third study builds upon the first two studies by linking the daily stress context to health outcomes over time. The allostatic load model specifies the relationship between chronic stress and biomarkers, and previous studies showed some association between chronic stress and
various health problems. Thus, this study extends the literature by providing insight into an important but largely unanswered question on stress biomarkers and their health implications. Some of the noticeable findings are the associations between biomarkers and health in the caregiving context, and the effect of ADS use on the biomarker-health associations.

**The subtleties of health disparity among caregivers**

The three studies confirm the fact that there are subtleties of health disparity among caregivers of IWDs. Caregiving is not a uniform experience. Despite the chronic stress associated with caregiving tasks, some caregivers manage daily challenges well and may have actually found caregiving an enriching experience (Freedman et al., 2014). Therefore, it is important to consider the contextual factors that define the nuances of caregiver well-being. ADS use and caregiving transitions were the only two contextual factors explored in this dissertation. We now know that the chronic stress of caregiving to IWDs is linked to neuroendocrine regulation of cortisol, DHEA-S, and sAA. In turn, the biomarkers of stress are associated with caregiver health over time. Such association is especially pronounced among caregivers who had a caregiving transition. ADS can be an effective respite to help buffer some of the physiological tolls of dementia caregiving. Thus, the restorative effect of ADS use can potentially make caregiving more manageable and sustainable.

The literature has suggested a number of factors associated with caregiver health and well-being. Among others, there are gender, age, ethnicity, caregiver-patient relationship types, psychosocial resources of social support and mastery, and objective and subjective primary stressors of caregiving. The stress-process model has primarily tested these factors using between-person designs. There is an emerging need to reevaluate these factors using within-person designs integrating both intensive and traditional longitudinal data. As within-person
processes can be different from between-person processes (Molenaar, 2004), the stress process model may be further revalidated or refined.

**Studying caregiving and caregiver well-being – the innovations**

This dissertation has applied some new methods in studying caregiving experiences and caregiver well-being. In addition to the basic growth curve models, we applied the spline growth curves to model diurnal cortisol and sAA trajectories. Also, we incorporated different time scales of daily diary and longitudinal measures over 12 months to study the association between daily biomarkers and health change over time. The advantages of these new methods include a better way to model change processes, and a better way to come up with research questions.

The growth curve model, a special application of hierarchical linear models or multilevel models, is a versatile and powerful tool to test some theoretical processes of change, or to explore some untheorized change processes and associations (Raudenbush & Bryk, 2002). On the one hand, it helps us to understand the many possible within-person processes of change; on the other hand, it helps us to explore and test for characteristics associated with different within-person change trajectories (Molenaar, 2004). Growth curve models can answer these two core questions of almost any change processes in the population: the first descriptive question about the patterns of change over time for some outcome of interest, and the second relational question about the association between predictors/covariates and the patterns of change.

Growth curve models are hierarchical in nature, making it an ideal tool to study within-person changes in relation to between-person differences. In *level-1*, within-person change over time is modeled. In *level-2*, between-person differences in change are modeled. The extent to which each individual manifests different patterns of within-person change, and the association with predictors is evaluated. The research questions can be mapped onto the linked pair of two
statistical models: a level-1 model, describing within-person change over time; and a level-2 model, relating predictors/covariates to any between-person differences in change.

In addition to the application of growth curve models in the daily context, it is also applied to study the relationships between biomarker and health change over a longer time span. To utilize data collected daily and over 12 months, we came up with a summary measure of daily biomarkers that was representative of daily neuroendocrine processes. Their health implication is then explored using growth curve models of health changes, a research question barely examined before. As shown in the three studies, there are different ways of estimating growth curves, depending on the time scale of the data being collected. The advantages of the spline models for intensively collected daily biomarkers are the following. They can model the daily profiles of concentration while account for the natural variability in the context of specific daily experiences. The samples do not have to be evenly distributed over the course of the day. Additionally, unequal number of samples from participants and variation in sampling time can be accommodated by such modeling approaches.

**The use of multiple health indicators**

In contrast to the single health measure approach adopted by much of the existing literature on caregiver physical health, this dissertation has considered two dimensions of caregiver health outcomes over a one-year period: functional limitations and bodily pain. Health is multi-dimensional, and this approach better captures comprehensive health changes in relation to caregivers’ everyday functioning. Some health outcomes to consider in future studies are sleep indicators and health behaviors such as physical activity and diet. Similarly, three biomarkers considered in this dissertation better captures neuroendocrine regulations compared
with the use of a single measure. The findings also confirm the distinct associations between
daily experiences, various biomarkers, and different health dimensions.

**Limitations**

In spite of its many contributions, this dissertation has some limitations. First, other
contextual factors known to influence caregiver health and well-being based on between-person
studies need to be explored using within-person designs. The stress process model that has been
guiding caregiving research may be modified to extend to the within-person daily settings. This
also calls for innovative designs in caregiving studies, such as time-series and measurement burst
designs. As caregiving is a varying phenomenon, the positive aspect of caregiving needs to be
emphasized and explored further.

Second, biomarkers from other bodily systems may further indicate caregiver health and
well-being beyond the neuroendocrine indicators. Some other biomarkers that mediate the
association between stress and health may be indicators of cardiovascular functioning (i.e.,
platelet activity, blood pressure, c-reactive protein, and endothelial function), and immunity
systems. They can be examined alone or in relation to caregiver affect, specific stressors of
caregiving (i.e., problem behaviors, and caregiving transitions), caregiving resources (i.e.,
mastery/self-efficacy, coping styles, and sleep), and health outcomes on older informal
caregivers of IWDs. Third, health outcome measures over a longer time span can be used to
specify health changes with precision. Other change function than linear trajectories can be
modeled to assist medical decisions and intervention efforts to best address caregivers’ health
care needs.

Family caregiving is essential for long-term services and supports system (LTSS); its
economic value to the country is immense (Reinhard et al., 2015). Family caregiving to IWDs
can be especially demanding and stressful than other type of caregiving. Because of the benefits to caregiver health and well-being, respite programs such as ADS should be made routinely available and affordable for caregivers who need the support. This dissertation joins the efforts along with public policy and private sectors towards a high quality LTSS system that everyone will eventually benefit.
REFERENCES


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