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Physiological and functional consequences of caregiving for relatives with dementia

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Abstract

Background—Chronic stress negatively affects health and well-being. A growing population of informal dementia caregivers experience chronic stress associated with extraordinary demands of caring for a relative with dementia. This review summarizes physiological and functional changes due to chronic dementia caregiver stress.

Methods—A literature search for papers assessing effects of dementia caregiving was conducted focusing on publications evaluating differences between caregivers and non-caregivers in objective measures of health and cognition.

Results—The review identified 37 studies describing data from 4145 participants including 749 dementia caregivers and 3396 non-caregiver peers. Objective outcome measures affected in dementia caregivers included markers of dyscoagulation, inflammation, and cell aging as well as measures of immune function, sleep, and cognition. Though diverse in designs, samples, and study quality, the majority of the studies indicated increased vulnerability of dementia caregivers to detrimental changes in health and cognition. Demographic and personality characteristics moderating or mediating effects of chronic stress in caregivers were also reviewed.

Conclusions—There is accumulating evidence that chronic dementia caregiver stress increases their vulnerability to disease and diminishes their ability to provide optimal care. Clinicians and society need to appreciate the extent of deleterious effects of chronic stress on dementia caregiver health.

Keywords

dementia caregivers; health; physiological marker; sleep quality; cognition

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Conflict of Interest

None.

Description of the authors' roles

Both authors contributed equally to the study concept and design including formulating research review questions, determining research strategy, reviewing and summarizing data, and writing the manuscript.

INTRODUCTION

The number of people with dementia is growing dramatically due to increased life expectancy, and about 70% of these people receive in-home care provided by family members (Thorpe, *et al.*, 2006). The demands of caregiving take a heavy toll on dementia caregivers' (DCG) physical and emotional health, often leading to more hospitalizations, higher medication usage, and greater mortality rate compared to non-caregiving peers (Vitaliano, *et al.*, 2003). DCG health problems are often neglected and overshadowed by those of their care recipient until a crisis occurs. However, DCG health and well-being are important to caregivers and their care recipient because they might impact the quality of care DCGs provide, the timing of nursing home placement of the care recipient, and overall healthcare costs (Vitaliano, *et al.*, 2003).

Multiple detrimental effects of caregiving on physical health have been brought to light previously in a meta-analysis that proposed to consider caregiving a health hazard (Vitaliano, *et al.*, 2003). The conclusions from that meta-analysis included the need for more research assessing physiological effects of caregiving. A decade later, the current review summarizes evidence highlighting the effects of dementia caregiving on health that has accumulated since 2003.

It is becoming clear that the DCG's vulnerability for health decline is not just due to caregiving duties but rather due to the chronic stress of caregiving. Indeed, compared to non-caregiving peers, caregivers in general and DCGs in particular typically experience significantly more stress (Gouin, *et al.*, 2012), which might be still underestimated depending on the assessment context because DCGs tend to report lower stress levels when assessed in a clinic than they do at home where they are providing care (Fonareva, *et al.*, 2012).

The current review focuses on health changes in DCGs compared to the trajectory of health changes in non-caregiving peers. Non-caregiving peers were chosen as a comparison group for DCGs due to these reasons: 1) This work aimed to assess effects of increased stress due to caregiving duties on health and function. Though DCG have more caregiving demands due to unpredictable nature of dementia and thus have higher risk for developing health problems, we believe that many caregiver stressors are common for different types of caregiver groups (e.g. caregivers to cancer patients, parent caregivers of chronically ill children etc.). Therefore, it might be difficult to disentangle the influence of dementia caregiving from the effect of other type of caregiving on health, but the effect of caregiving stress can be more readily observed when comparison is a peer group without caregiving duties. 2) It was important to have the comparison group that is close in age to DCGs because age has a strong influence on physiologic and cognitive health. Many caregiver groups (e.g. caregivers to cancer patients etc.) are too heterogeneous on this variable. Caring for a relative with any health problem might negatively affect caregiver's health; however, family caregivers of dementia patients are a growing population who face additional caregiving challenges associated with the chronic, debilitating, and incurable nature of the disease along with the progressive mental loss in their care recipient (Vitaliano, *et al.*, 2003). The diverse sources of DCG stress include excessive time constraints, increased chores, behavioral management issues of the person with dementia (PWD), and anticipatory grieving.

The primary goal of this review is to increase researchers' and clinicians' awareness of physical and psychological risks associated with dementia caregiving. To avoid potential bias associated with self-reported subjective measures, the major emphasis of this review is on addressing changes in DCG health and function assessed objectively (i.e. not self-

reported). This review also discusses mediating and moderating factors that have emerged from DCG research to date.

METHODS

Data sources and search strategy

Electronic searches were conducted using MEDLINE, PsycINFO, Global Health, EBM reviews Cochrane Database of Controlled Trials, and EBM reviews Cochrane Database of Systematic Reviews databases to identify relevant papers published between January 2001 and January 2012. The search terms are described in Table 1. The search was limited to publications in English, with duplicates removed. As Figure 1 indicates, the initial search yielded 239 publications. The abstracts of the publications encompassed by the search were reviewed by both authors for the content. The details of the search flow are presented in Figure 1.

Study Eligibility

To be included, the studies had to meet the following criteria: 1) caregivers of patients with dementia were assessed, 2) DCGs were compared to age- and gender-matched non-caregiving controls, 3) study outcomes included objective (i.e. not self-reported) measures. Studies focusing on bereavement issues, interventional studies, and studies published in languages other than English were excluded. Next, relevant publications were cross-referenced for additional articles on the topic yielding the total of 37 publications included in the review.

Data extraction

The data extracted from the reviewed publications included: 1) study author names, 2) publication dates, 3) study designs (e.g. cross-sectional, longitudinal) and follow-up period for longitudinal studies, 4) group sample sizes, 5) mean age or age ranges for the groups, 6) gender distributions, 7) percent of spousal caregivers in the DCG group, 8) primary objective outcomes used (e.g., biological samples, sleep architecture, cognitive functioning), 9) secondary outcomes, objective or subjective, 10) results of analyses assessing between-group differences on most relevant outcomes and factors affecting the relationship between caregiving and health.

RESULTS

Study characteristics

The review identified 37 studies describing data from 4145 participants including 749 DCGs and 3396 non-DCG peers or controls (CTL). The majority ($n = 35$) of the studies included in the review were conducted in the United States; one study was completed in Netherlands, and one in Brazil. The studies included in the review were published between 2003 and 2012. Twenty-two of the selected 37 studies demonstrated significant differences between DCGs and controls in objective measures of health, sleep, or cognition, with DCGs affected in a detrimental way. Additionally secondary analyses in the included studies indicated moderating and mediating factors associated with detrimental health or cognitive changes in DCGs.

Outcome measures assessed in the included studies

Physiological markers indicative of stress and associated with health problems were assessed as primary outcomes in twenty-three of the reviewed studies (Aschbacher, *et al.*, 2005; Brummett, *et al.*, 2008; Brummett, *et al.*, 2005; Damjanovic, *et al.*, 2007; de Vugt, *et*

al., 2005; Epel, *et al.*, 2010; Gouin, *et al.*, 2012; Kiecolt-Glaser, *et al.*, 2011; Kiecolt-Glaser, *et al.*, 2003; Mausbach, *et al.*, 2010; Mausbach, *et al.*, 2007; McCallum, *et al.*, 2006; Mills, *et al.*, 2004; O'Donovan, *et al.*, 2012; Roepke, *et al.*, 2011a; Roepke, *et al.*, 2011b; Segerstrom, *et al.*, 2008; Tomiyama, *et al.*, 2012; von Kanel, *et al.*, 2012b; von Kanel, *et al.*, 2011; von Kanel, *et al.*, 2008; von Kanel, *et al.*, 2012a; Wahbeh, *et al.*, 2008). The specific categories of physiological markers evaluated in the reviewed studies included markers of: 1) sympathetic nervous system activity, 2) health and metabolism, 3) coagulant activity, 4) hypothalamic-pituitary-adrenal (HPA) axis activity, 5) immune function, and 6) cellular aging. Objectively evaluated sleep parameters were primary outcomes in four of the selected studies (Castro, *et al.*, 2009; Fonareva, *et al.*, 2011; McKibbin, *et al.*, 2005; Rowe, *et al.*, 2008). Three studies evaluated both physiological markers and sleep parameters as outcome variables (Mills, *et al.*, 2009; von Kanel, *et al.*, 2010; von Kanel, *et al.*, 2012c). Performance on cognitive tests or diagnosis of cognitive impairment were used as outcome measures in seven of the selected studies (Caswell, *et al.*, 2003; de Vugt, *et al.*, 2006; Norton, *et al.*, 2010; Oken, *et al.*, 2011; Palma, *et al.*, 2011; Vitaliano, *et al.*, 2005; Vitaliano, *et al.*, 2009). Specific outcome measures and major findings for each study are described in Tables 2 and 3 (studies assessing physiological markers), Table 4 (studies assessing sleep variables), and Table 5 (studies assessing cognitive function).

Quality assessment of the included studies

Study design—Study designs of the selected studies included case control ($n = 18$), cross-sectional ($n = 8$), population-based ($n = 1$), correlational post hoc review ($n = 1$), or longitudinal ($n = 9$) studies. Follow-up periods for DCGs in longitudinal studies ranged between 1 and 6 years.

Sample size—Median sample size was 44 for DCGs and 63 for non-DCG peers. Some of the data described in the studies came from the same sample. Therefore, some of the observations from the research conducted to date are not independent.

Participant selection, confounding, and bias—Recruiting DCGs for research studies is difficult due to time constraints in this population. Therefore DCGs participating in the research are typically high functioning and generally healthy individuals and might not be representative of the general DCG population. Most of the studies included in the review assessed primarily female DCGs. Only one study included exclusively males (Brummett, *et al.*, 2008), and one study assessed the role of gender in changes associated with caregiving (Mills, *et al.*, 2009).

The age of DCG participants included in the studies ranged between 50 and 89 years, with the majority of studies evaluating DCGs in 60s and 70s. Only one study investigated age effects in producing changes associated with caregiving (Palma, *et al.*, 2011). Furthermore, the majority of DCGs were spouses or partners of the PWD, making it difficult to generalize the findings to DCGs who are children or other PWD relatives.

Other important factors that are likely to influence health and well-being of DCGs including the severity of the PWD symptoms, length of caregiving, frequency of using respite care, and socioeconomic status were not consistently evaluated by the majority of the studies included in this review.

Dementia caregiving effects on physiological markers of health

Several categories of physiological biomarkers and health risk factors have been compared between DCGs and controls. The reviewed physiological biomarkers are often linked to the conditions of particular concern in DCGs compared to general population, such as

hypertension, cardiovascular disease (CVD), hyperglycemia, immune dysfunction, and overall mortality (von Kanel, *et al.*, 2008). Tables 2 and 3 contain information about the studies described in this section evaluating differences between DCGs and controls on physiological markers.

Markers of sympathetic nervous system activity—Sympathetic nervous system is one of the first to activate in response to stress, causing downstream effects on blood pressure (BP), catecholamine levels, and β_2 adrenergic receptors. These markers are affected in DCGs, according to several studies included in the review.

DCGs have higher systolic (von Kanel, *et al.*, 2008) and diastolic (Roepke, *et al.*, 2011b) BP than controls (effect sizes between .36 and .84 using Cohen's d) even though more DCGs use antihypertensive medications (von Kanel, *et al.*, 2008). Additionally, BP moderates the rate of change in glomerular filtration rate in DCGs with increased sympathetic activation after major transition such as PWD nursing home placement (von Kanel, *et al.*, 2012b). Other markers of sympathetic nervous system activation, β_2 adrenergic receptor sensitivity and density, are typically lower in DCGs reporting greater DCG stress (Mills, *et al.*, 2004). In particular, lymphocyte β_2 adrenergic sensitivity and density are significantly reduced in vulnerable DCGs who provide over 12 hours of daily care with less than one hour of respite care in the previous 6 months, but not in DCGs who use respite care once or more per month (Mills, *et al.*, 2004).

Markers of health and metabolism—Biomarkers of metabolism, hepatic function, and endothelial function are often affected in DCGs. The risk for presence of carotid plaque is significantly greater in DCGs and is twice that of controls (Roepke, *et al.*, 2011a). DCGs also have a higher clinically relevant risk of developing coronary heart disease over 10-years in DCGs than controls with a medium size effect of .57 using Cohen's d (von Kanel, *et al.*, 2008). Some studies report group differences between DCGs and CTLs in allostatic load scores (Roepke, *et al.*, 2011b) and cardiometabolic risk (von Kanel, *et al.*, 2011) that fall short of conventional statistical significance but indicate a trend with low to moderate effect sizes (Cohen's d between .28 and .38).

Several of the reviewed studies suggest variables that can increase DCGs' vulnerability to developing health problems. For example, glucose metabolism markers such as fasting plasma glucose and glycosylated hemoglobin are elevated in DCGs who reside in neighborhood they perceive as unsafe compared to controls living in similar neighborhoods, but DCGs living in better neighborhoods are no different from controls on these measures (Brummett, *et al.*, 2005). Dementia severity of the PWD also impacts DCG health markers. An endothelial function measure, brachial artery flow-mediated dilation, is impaired in DCGs of a spouse with moderate to severe dementia but not in DCGs of a spouse with mild dementia or controls (Mausbach, *et al.*, 2010). Some new markers such as glomerular filtration rate have also been tested. Though not different between DCGs and controls, this marker decreases after major life transition in DCGs with high BP (von Kanel, *et al.*, 2012b).

Markers of coagulant activity—Procoagulant activity is linked to risk for future cardiac events, and, given DCG's vulnerability to CVD, several investigations focused on coagulation markers in DCGs, highlighting significant changes in coagulant activity due to DCG stress. D-dimer, a commonly used marker of fibrin formation and degradation, is typically higher in DCGs than non-DCGs (Aschbacher, *et al.*, 2005; von Kanel, *et al.*, 2005). Several studies indicate that D-dimer levels relate to gender, PWD dementia severity, DCG sleep quality, and coping methods used by DCG (Aschbacher, *et al.*, 2005; Mills, *et al.*, 2009; von Kanel, *et al.*, 2010).

Another coagulant activity marker, plasma levels of tissue-type plasminogen activator antigen, a risk factor for coronary heart disease, shows a significant increase in DCGs over 5 years, and the rate of increase in the level of this marker is 3 times greater in DCGs than controls (Mausbach, *et al.*, 2007). This increase is significant even after controlling for body mass index, BP, age, gender, and CVD medications (Mausbach, *et al.*, 2007).

Research suggests that the acute procoagulant stress response might constitute a dynamic mediator of allostatic load, a measure of dysregulation and cumulative cost of stressors presented to an organism linked to increased risk of CVD; and allostatic load is higher in DCGs than non-DCGs (Roepke, *et al.*, 2011c).

Markers of hypothalamic-pituitary-adrenal (HPA) axis activity—HPA axis is a part of the neuroendocrine system mediating reactions to stress. Its function is assessed using measures of cortisol reactivity and circadian patterns. Circadian cortisol patterns, particularly cortisol awakening stress response, are different in DCGs compared to non-DCGs, with medium to moderate effect size of .70 using Cohen's *d* (de Vugt, *et al.*, 2005; Wahbeh, *et al.*, 2008). Additionally, DCGs have increased cortisol levels at 10 pm compared to non-DCGs, and such elevated bedtime cortisol levels are associated with performance deficits on a memory task (Palma, *et al.*, 2011).

Cortisol levels in DCG population are affected by many factors such as age, PWD symptom severity, telomere length, and overall health (de Vugt, *et al.*, 2005; McCallum, *et al.*, 2006; Tomiyama, *et al.*, 2012). Ethnicity also emerges as a predictor of cortisol slope: African American DCGs have a flattened diurnal cortisol secretion patterns (linked to subclinical disease and increased mortality from cancer) compared to European American DCGs (McCallum, *et al.*, 2006).

Recent efforts to identify genetic factors linked to stress result in proposing candidate genes linked to HPA function in males (Brummett, *et al.*, 2008). Specifically, male DCGs with monoamine oxidase-A gene promoter-uVNTR alleles linked to less transcriptional activity have cortisol activity patterns indicative of HPA blunting compared to DCGs with more active alleles and to controls (Brummett, *et al.*, 2008).

Markers of immune function—Natural aging effects on immune function are amplified by chronic stress, and thus immune markers are important to study in DCGs. Four out of five reviewed studies assessing immune function markers as primary outcomes indicate significant changes in DCGs' immune function compared to controls (Gouin, *et al.*, 2012; Kiecolt-Glaser, *et al.*, 2003; Segerstrom, *et al.*, 2008; von Kanel, *et al.*, 2012b). For example, DCGs experience more stressors within a 24-hour period than non-DCGs, and this occurrence of multiple daily stressors is linked to increased serum interleukin (IL)-6 and C-reactive protein (CRP) levels (Gouin, *et al.*, 2012). Moreover, DCG rate of increase in IL-6 levels is 4 times larger than that of non-DCGs, and this IL-6 increase is sustained in DCGs even after the PWD death (Kiecolt-Glaser, *et al.*, 2003). Further, DCGs show a prolonged increase in IL-6 levels compared to controls after receiving influenza vaccine, and the IL-6 levels are predicted by negative repetitive thoughts (Segerstrom, *et al.*, 2008). Overproduction of IL-6 is linked to many age-related problems including CVD, diabetes, cancer, and Alzheimer's disease functional decline (Kiecolt-Glaser, *et al.*, 2003; Segerstrom, *et al.*, 2008). Not all studies observe differences in IL-6 levels between DCGs and controls (Fonareva, *et al.*, 2011; Mills, *et al.*, 2009), but there is more agreement about CRP levels being increased in DCGs with moderate effect sizes between .39 and .44 using Cohen's *d* (Fonareva, *et al.*, 2011; Gouin, *et al.*, 2012).

Further, there is also a tendency for DCGs to have greater tissue necrosis factor-alpha (TNF- α) levels compared to controls (Damjanovic, *et al.*, 2007; Kiecolt-Glaser, *et al.*, 2011). Over time DCGs may have a 16 % increase in TNF- α levels compared to non-caregiving controls (von Kanel, *et al.*, 2012b). Moreover, cessation of DCG duties results in a decreased inflammatory state: three months after PWD's death inflammation in former DCGs is lower compared to that of acting DCGs (von Kanel, *et al.*, 2012b). TNF- α also moderates the relationships between caregiving and sleep quality parameters, with DCGs displaying high TNF- α levels suffering from poorer sleep quality compared to DCGs whose TNF- α levels are higher (von Kanel, *et al.*, 2012c).

Markers of cellular aging—Telomere length and telomerase activity are markers of immune cell aging. Chronic stress affects these markers and speeds up the process of cellular aging (Tomiya, *et al.*, 2012). DCGs have lower T cell proliferation and higher production of immune-regulatory cytokines than controls in response to stimulation in vitro (Damjanovic, *et al.*, 2007). Further, DCGs have shorter telomeres and higher basal telomerase activity than non-caregiving peers, suggesting an unsuccessful attempt of cells to compensate for the excessive loss of telomeres (Damjanovic, *et al.*, 2007). The reviewed studies suggest a moderate to high effect size (Cohen's *d* between .48 and 2.0) for group differences in telomere length (Damjanovic, *et al.*, 2007; Kiecolt-Glaser, *et al.*, 2011).

In addition to telomeres being generally shorter in DCGs than in controls, (Damjanovic, *et al.*, 2007; Kiecolt-Glaser, *et al.*, 2011), telomerase activity in DCGs is lower across time compared to controls (Epel, *et al.*, 2010). These effects of chronic DCG stress on markers of inflammation and cell aging can be magnified by childhood exposure to abuse or adversity (Kiecolt-Glaser, *et al.*, 2011). Additionally, caregiving exerts an indirect effect on telomere length through anticipatory threat appraisal that is greater in DCGs exposed to acute stressor (O'Donovan, *et al.*, 2012). Recent research demonstrates that telomerase activity is sensitive to acute stressors, linked to cortisol changes, and can be affected by psychological response to tasks (such as threat perception) (Epel, *et al.*, 2010).

Overall, the majority (14 out of 26) of reviewed studies indicate that physiological markers of health are more negatively affected in DCGs than controls. The strongest evidence is available, according to this review, for the markers of immune function and cellular aging, as well as for cardiovascular risk factors.

Functional changes due to caregiving stress

In addition to changes in physiologic markers that might not be apparent to DCGs without special testing on biological samples, several noticeable changes in functioning including changes in sleep quality and cognitive performance are typical in DCGs when compared to non-caregiving peers.

Sleep quality—Poor sleep quality is a common complaint in DCGs, who report more sleep problems than controls and rate their sleep quality similar to that of insomnia sufferers (Fonareva, *et al.*, 2011). Some of the reviewed studies suggest that DCGs misperceive severity of PWD's and their own sleep problems (Castro, *et al.*, 2009; von Kanel, *et al.*, 2012c). However, DCG sleep deficits have been confirmed with objective sleep assessments, using actigraphy and polysomnography, indicating that DCGs have decreased sleep efficiency, longer sleep latency, and spend less of their sleep time in more restful sleep stages (Fonareva, *et al.*, 2011; Rowe, *et al.*, 2008; von Kanel, *et al.*, 2010). Sleep latency, in particular, in two of the reviewed studies, has been shown to have effect sizes ranging from .49 to .69 using Cohen's *d*, indicating moderate effects. In one study, however, the groups did not differ on objectively assessed sleep latency, with Cohen's *d* of .27 (Castro, *et al.*,

2009). The largest effect size of 1.26 using Cohen's *d* in the reviewed studies has been reported for sleep efficiency (Rowe, *et al.*, 2008), but this finding has not been corroborated by other studies.

Predictors of sleep quality include DCG-related factors such as age, gender, depressive symptoms, physical function, levels of inflammatory markers, and stress, as well as tendency to use criticism as a behavioral management strategy (Fonareva, *et al.*, 2011; McKibbin, *et al.*, 2005; Mills, *et al.*, 2009; Rowe, *et al.*, 2008). PWD-related factors such as dementia severity (Mills, *et al.*, 2009) and PWD sleep disturbances (Castro, *et al.*, 2009) also affect DCG sleep. PWD sleep problems are often cited among major reasons for seeking permanent PWD institutionalization; however, PWD placement does not always leads to improvements in DCG sleep, and PWD death can lead to greater severity of DCG sleep disturbances (von Kanel, *et al.*, 2012b) indicating that sleep is affected by many factors. More information about the studies assessing DCG sleep quality with objective measures is available in Table 4.

Cognitive function—Cognitive health is important for DCG's quality of life and well-being and vital for PWD care quality. Therefore it is of concern that the reviewed studies show that DCGs perform worse than age-matched controls on cognitive tasks of general cognitive processing, delayed verbal recall, and executive function, with the effects sizes (Cohen's *d*) ranging from .38 to .49, indicating small to medium effects (de Vugt, *et al.*, 2006; Oken, *et al.*, 2011). Performance on measures assessing attention, concentration, and processing speed is significantly affected in DCGs in four of the reviewed studies (Caswell, *et al.*, 2003; de Vugt, *et al.*, 2006; Oken, *et al.*, 2011; Vitaliano, *et al.*, 2009), with the effect sizes ranging from .38 to .77 using Cohen's *d*, indicating moderate to large effects. Additionally, compared to the general population, DCGs are at increased risk of developing dementia, according to a population-based study of over 1,000 couples. This study suggests that spouses of dementia patients are at an increased risk of developing dementia compared to non-caregiving spouses, after controlling for gender, age, ApoE genotype, and socioeconomic status (Norton, *et al.*, 2010). Furthermore, male DCG spouses have about a 12-fold increase in risk and female DCG spouses have about a four-fold increase in risk for developing dementia than CTLs (compared to about five-fold increase in this risk due to the presence of 2 ApoE ϵ 4 alleles) (Norton *et al.*, 2010).

Even minimal cognitive problems in DCGs affect their ability to provide adequate care (de Vugt, *et al.*, 2006; Vitaliano, *et al.*, 2009). For example, DCGs' low performance on verbal memory tasks is related to decreases in caregiving competency, which may lead to increases in PWD dementia behavioral symptoms, such as hyperactivity (de Vugt, *et al.*, 2006). Greater PWD behavioral problems lead to greater DCG stress, which, in turn, may cause more cognitive deficits. This can become a viscous cycle. Of interest, all seven studies assessing cognitive function included in the review showed a significant vulnerability of DCGs cognitive function compared to that of age-matched controls. Though the reviewed studies used heterogeneous cognitive assessments, measures of attention and processing speed have been tested in more than one study and seem to be particularly affected by caregiving. Table 5 contains information about the studies assessing DCG cognitive function.

Proposed moderators and mediators of stress-related health consequences

In addition to comparisons between DCG and control samples on objective measures of health and function, several factors that can influence the relationship between caregiving stress and health have emerged. Below we briefly review some of the known risk and

protective factors that affect relationship between caregiving and health, along with the evidence available from the reviewed studies.

Risk Factors

DCG characteristics—Several of the reviewed studies indicate that DCG's vulnerability to developing health and functional problems can be affected by age, gender, ethnic and cultural background, residence neighborhood, childhood experiences of abuse, physical activity level, and utilization of respite care (Kiecolt-Glaser, *et al.*, 2011; Mausbach, *et al.*, 2008; McCallum, *et al.*, 2006; Segerstrom, *et al.*, 2008; von Kanel, *et al.*, 2011). One study suggests that DCGs' genetic make-up might predispose some DCGs to a greater risk for developing health problems in the face of stress (Brummett, *et al.*, 2008). While some of these factors are unchangeable, some, such as physical activity and respite care utilization, should be encouraged in DCGs.

PWD characteristics—Severity of the PWD symptoms is among the most important contributors to a DCG burden. Current review indicates that PWD characteristics including duration of illness, dementia severity, behavioral symptoms, and sleep patterns (Castro, *et al.*, 2009; de Vugt, *et al.*, 2005; Mausbach, *et al.*, 2010; Mills, *et al.*, 2009) can increase DCGs risk for developing health and functional problems. Pharmacological therapies for a PWD for sleep and behavioral problems might be advantageous to the DCG well-being. Regular use of coping strategies, especially problem-focused strategies, by DCGs is also associated with slower disease progression in PWD (Tschanz, *et al.*). Therefore, educating a DCG of a newly diagnosed PWD with this information might be beneficial to both the DCG and PWD.

DCG depression—Vulnerability to major depressive disorder, the most documented risk factor for increased health problems, is common in DCGs (Vitaliano, *et al.*, 2009), with prevalence of depression in DCGs reaching 30–80% compared to 6–9% in general population of adults over 55 (Schoenmakers, *et al.*, 2010). However, symptoms are underreported, which leads to a lack of treatment and results in diminished quality of life. Only 25% of DCGs acknowledge being depressed when interviewed, yet when assessed with a depression scale, about 55% in the same DCG sample receive a score indicative of clinical level of depression (Clark, *et al.*, 2011). According to the study included in the review, depressed mood mediates slowing of cognitive processing in DCGs (Vitaliano, *et al.*, 2009). Other cognitive function mediators in DCGs emerging from the reviewed studies are hostility, metabolic risk, self-perceived distress and sleep impairment (Caswell, *et al.*, 2003; Oken, *et al.*, 2011; Vitaliano, *et al.*, 2005).

Protective factors

Recently the focus of research has been expanded to include not only risk factors for health problems in DCGs but also to identify factors that buffer negative effects of DCG stress.

Of most interest are the factors, including DCG traits and skills, that can be changed through education or training. For example, personal mastery, a concept similar to self efficacy, reflecting one's belief in the ability to manage life's obstacles, negatively correlates with norepinephrine reactivity to acute psychological stressor in DCGs (Roepke, *et al.*, 2008). However, in one study greater DCG mastery was linked to a greater allostatic load score (Roepke, *et al.*, 2008), so more studies are needed to fully understand the role of personal mastery and self efficacy in DCG health.

Lifestyle factors such as diet and physical activity are also important. One of the reviewed studies indicates that physical activity can moderate the relationship between DCG status

and cardiometabolic risk (von Kanel, *et al.*, 2011). Additionally, the effects of DCG stress might be influenced by relationship closeness between DCG and their PWD, with greater baseline closeness associated with better functioning and lower depression in the early phases of caregiving but with greater losses in functioning later on (Fauth, *et al.*, 2012).

Physiological effects of caregiving are more related to perceived stress than the work of being a DCG (Epel, *et al.*, 2010). Relationships between caregiving and health might be affected by stress reactivity that is often linked to DCG status: e.g. neuroticism, a trait related to increased stress reactivity, is higher in DCGs than controls (Oken, *et al.*, 2011). Another construct related to reactivity to stress, the non-judgmental mindfulness (i.e., not associating a negative emotion to an event) also differs between DCGs and controls (Oken, *et al.*, 2011). The DCG and non-caregiver differences in these traits indicate that aspects of stress reactivity are altered by environmental influences and can be targeted in interventions.

DISCUSSION

The results of this review demonstrate that there has been substantial research documenting effects of chronic DCG stress on health-related outcomes and cognitive function, and the evidence has accumulated significantly since the prior review (Vitaliano, 2003). The objective outcome measures used in the reviewed studies include markers of sympathetic, hypothalamic-pituitary-adrenal axis and coagulant activity, measures of metabolic and immune functioning and cellular aging. Additionally, some of the reviewed studies investigated DCG function by objectively measuring DCG sleep quality and cognitive performance. Overall, the majority of reviewed studies indicate that physiological markers of health as well as cognitive function and sleep quality are more negatively affected in DCGs than controls. The strongest evidence to date is available for measures of immune and cellular aging markers, cardiovascular risk factors, sleep quality, and cognition.

One of the most important outcomes of this review is the presence of obvious deficits in DCGs compared to controls on several cognitive domains including processing speed, attention, memory, and executive functions (de Vugt, *et al.*, 2006; Oken, *et al.*, 2011; Vitaliano, *et al.*, 2009). It is alarming that DCGs perform worse than controls on several cognitive tasks because optimal cognitive health is critical for DCGs who, in addition to managing their own affairs, also assume responsibility for the PWD welfare. Even more alarming, one study reported that compared to general population, DCGs are at increased risk of developing dementia (Norton, *et al.*, 2010). Though there are shared environmental risk factors for married couples including socioeconomic status, diet, education and activity levels, the contribution of direct physiological effects of DCG burden and stress on cognition needs to be evaluated as a potential mediator, and the intriguing finding of DCG increased risk for developing dementia needs to be confirmed by future studies.

Another important outcome of this review is the list of potential factors that can modify DCG effect of health and function. Understanding factors affecting relationships between caregiving stress and health can help design and target optimal interventions.

Several characteristics common in DCGs emerge as moderating or mediating factors. In addition to previously known influences of age, SES, and PWD characteristics on DCG health, studies in this review show that access to respite and physical activity levels can also affect the relationship between DCG stress and health (Mills, *et al.*, 2004; von Kanel, *et al.*, 2011). Other factors lifestyle factors are also of interest and need to be assessed in the future. Caregiving involves constant supervision of the PWD, which requires countless amounts of time and energy, and DCGs often neglect their own health, diet, sleep, and exercise routines. More research evaluating effects of these factors on caregiving and health

is warranted. Further, resilience traits such as self-efficacy and mastery might buffer detrimental effects of chronic DCG stress and need to be investigated further as potentially promising for future interventions. Another interesting finding from a single study that emerge from the review is potential genetic influences on DCG stress reactivity (Brummett, *et al.*, 2008). This finding needs to be confirmed and extended in future research.

A common DCG issue not addressed in the reviewed studies is social isolation. Caucasian DCGs are especially prone to social isolation compared to African American or Latino DCGs who traditionally rely on extended family networks (Schoenmakers, *et al.*, 2010). Both ethnicity factors and isolation are critical to assess in the future as they might increase the risk of DCG depression (Schoenmakers, *et al.*, 2010). Further, though this review mentioned depression as a common DCG risk factor, efficacy of depression treatments in the context of the chronic stressor of dementia caregiving and best treatment approaches for depression in DCGs remained beyond the scope of this review and should be addressed in future work.

Knowledge of DCGs' vulnerabilities as well as mediating and moderating factors, both increasing and decreasing risk of developing health problems in DCGs, is critical for improving DCG treatments and for optimizing DCG quality of life. Targeting PWD problematic behavior, as well as DCG sleep, physical activity, and support including access to respite care might be promising. Next, interventions influencing DCG stress reactivity and resilience traits are of great interest and potential.

Limitations and future directions

There are several limitations to this review. First, the literature search included only papers written in English, leaving out relevant work published in other languages. Next, some papers could possibly have been omitted due to the specifics of the search strategy: studies describing DCG interventions were excluded from this review even if objective measures were evaluated. The reasons for this exclusion were: 1) the aim of this review was to assess effects of dementia caregiving on health and physiology rather than assess changes resulting from interventions and 2) we were not able to locate interventional studies where DCG were compared to non-DCG. The studies focusing on issues associated with bereavement after PWD death were also excluded, but potential synergistic effects of chronic DCG stress and bereavement are targets for future research.

Another limitation is the observational nature of the reported studies since it is not feasible to assign participants to DCG and control conditions randomly. Thus, there is a risk of bias in the studies comparing DCGs and non-DCGs that diminishes the level of evidence obtained from the research studies.

Most of the reviewed studies were observational case-control or cross-sectional studies along with several longitudinal studies. This prevents conclusions regarding causal effects of caregiving. Also, in most cases, the designs of the reported studies did not include assessor's blinding to the DCG status, potentially biasing the outcome assessments. Next, many of the reported studies were conducted by few laboratories interested in DCG issues, potentially affecting the generalizability of the summarized findings.

Furthermore, the majority of the reported studies recruited primarily female participants, with only a small number of studies assessing the effect of gender on the relationship between caregiving and health. Therefore, the findings reported in this work are relevant to female DCGs, but it is unclear how they can generalize to male DCGs. Similarly, the majority of the reviewed studies were conducted in the US with Caucasian participants, and

the generalizability of the reported findings to other ethnic and cultural groups remains unknown.

Further, this review focused on published studies and did not include any data from unpublished theses or abstracts relevant to the topics of interest. There is a known positive result publication bias and, therefore, this review might be skewed in favor of the studies demonstrating significant differences in DCGs compared to non-caregivers.

The choice of DCG comparison group is another potential limitation. In this review we chose to discuss comparisons between the groups of DCGs and non-caregiving peers. Comparing DCG and caregivers of people with conditions other than dementia is an important topic for future reviews.

Lastly, unlike the previous review by Vitaliano (2003), this review did not include meta-analysis thus preventing many generalized conclusions from the evidence. The authors did not believe that using meta-analytic techniques for this work would be appropriate the studies in this review due to heterogeneity in the outcome measures (e.g. physiological assays vs. sleep architecture vs. cognitive performance) and due to differences in sensitivity among the outcome measures used for assessing a specific function (e.g. using different cognitive tests to test cognitive health).

The current work highlighted the importance of investigating the extent of cognitive deficiencies in DCGs and their risk for developing dementia in future studies. Since there is worse cognition among DCGs compared to controls, future efforts should be directed to understanding the mechanism of cognitive decline due to caregiving. Future research should also assess the validity of the current findings for male DCGs and DCGs of ethnic and cultural backgrounds other than white representatives of Western culture. It is important to continue identifying individual DCG characteristics affecting the relationship between caregiving stress and health. Specifically, continuing assessment of candidate mediating and moderating factors that are amenable to change in DCG is critical for designing effective interventions.

CONCLUSIONS

Despite the above limitations, this review highlights the current state of research dedicated to understanding the effects of dementia caregiving on DCG health.

There is a growing recognition that chronic stress experienced by DCGs is linked to many physiological changes and changes in behavior and function. Clinicians often consider DCGs healthy adults not requiring special care. DCGs also often neglect their own health by limiting their visits to care providers for their own needs and failing to obtain vaccinations (Thorpe, *et al.*, 2006). Accumulating evidence points to the fact that it might be useful to start viewing caregiving as a health hazard, as originally proposed by Vitaliano and colleagues (2003). The public, clinicians, DCG families, and DCGs, need to be educated about the risks involved in dementia caregiving to allow for timely intervention or prevention of the potential problems in DCGs. Societal resources, which are always limited, need to be optimally allocated to maximize the health and well-being of DCGs.

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References

- Aschbacher K, et al. Coping processes and hemostatic reactivity to acute stress in dementia caregivers. *Psychosomatic Medicine*. 2005; 67:964–971. [PubMed: 16314602]
- Brummett BH, et al. Neighborhood characteristics moderate effects of caregiving on glucose functioning. *Psychosomatic Medicine*. 2005; 67:752–758. [PubMed: 16204434]
- Brummett BH, et al. HPA axis function in male caregivers: effect of the monoamine oxidase-A gene promoter (MAOA-uVNTR). *Biological Psychology*. 2008; 79:250–255. [PubMed: 18639608]
- Castro CM, et al. Sleep patterns and sleep-related factors between caregiving and non-caregiving women. *Behavioral Sleep Medicine*. 2009; 7:164–179. [PubMed: 19568966]
- Caswell LW, et al. Negative associations of chronic stress and cognitive performance in older adult spouse caregivers. *Experimental Aging Research*. 2003; 29:303–318. [PubMed: 12775440]
- Clark MC, Nicholas JM, Wassira LN, Gutierrez AP. Psychosocial and Biological Indicators of Depression in the Caregiving Population. *Biological Research for Nursing* retrieved February. 2011; 15:2012. from <http://brn.sagepub.com/content/early/2011/07/05/1099800411414872>.
- Damjanovic AK, et al. Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. *Journal of Immunology*. 2007; 179:4249–4254.
- de Vugt ME, et al. Behavioral problems in dementia patients and salivary cortisol patterns in caregivers. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 2005; 17:201–207. [PubMed: 15939974]
- de Vugt ME, et al. Cognitive functioning in spousal caregivers of dementia patients: findings from the prospective MAASBED study. *Age and Ageing*. 2006; 35:160–166. [PubMed: 16495293]
- Epel ES, et al. Dynamics of telomerase activity in response to acute psychological stress. *Brain, Behavior, and Immunity*. 2010; 24:531–539.
- Fauth E, et al. Caregivers' relationship closeness with the person with dementia predicts both positive and negative outcomes for caregivers' physical health and psychological well-being. *Aging Ment Health*. 2012; 16:699–711. [PubMed: 22548375]
- Fonareva I, Amen AM, Ellingson RM, Oken BS. Differences in stress-related ratings between research center and home environments in dementia caregivers using ecological momentary assessment. *International Psychogeriatrics*. 2012:1–9.
- Fonareva I, Amen AM, Zajdel DP, Ellingson RM, Oken BS. Assessing sleep architecture in dementia caregivers at home using an ambulatory polysomnographic system. *Journal of Geriatric Psychiatry and Neurology*. 2011; 24:50–59. [PubMed: 21320949]
- Gouin JP, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser J. Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology*. 2012; 31:264–268. [PubMed: 21928900]
- Kiecolt-Glaser JK, et al. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proceedings of the National Academy of Sciences of the United States of America*. 2003; 100:9090–9095. [PubMed: 12840146]
- Kiecolt-Glaser JK, et al. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. *Psychosomatic Medicine*. 2011; 73:16–22. [PubMed: 21148804]
- Mausbach BT, et al. Spousal caregivers of patients with Alzheimer's disease show longitudinal increases in plasma level of tissue-type plasminogen activator antigen. *Psychosomatic Medicine*. 2007; 69:816–822. [PubMed: 17942832]
- Mausbach BT, et al. A 5-year longitudinal study of the relationships between stress, coping, and immune cell beta(2)-adrenergic receptor sensitivity. *Psychiatry Research*. 2008; 160:247–255. [PubMed: 18708265]
- Mausbach BT, et al. Association between chronic caregiving stress and impaired endothelial function in the elderly. *Journal of the American College of Cardiology*. 2010; 55:2599–2606. [PubMed: 20513601]
- McCallum TJ, Sorocco KH, Fritsch T. Mental health and diurnal salivary cortisol patterns among African American and European American female dementia family caregivers. *The American Journal of Geriatric Psychiatry*. 2006; 14:684–693. [PubMed: 16861373]

- McKibbin CL, et al. Sleep in spousal caregivers of people with Alzheimer's disease. *Sleep*. 2005; 28:1245–1250. [PubMed: 16295209]
- Mills PJ, et al. Vulnerable caregivers of Alzheimer disease patients have a deficit in beta 2-adrenergic receptor sensitivity and density. *The American Journal of Geriatric Psychiatry*. 2004; 12:281–286. [PubMed: 15126229]
- Mills PJ, et al. Effects of gender and dementia severity on Alzheimer's disease caregivers' sleep and biomarkers of coagulation and inflammation. *Brain, Behavior, and Immunity*. 2009; 23:605–610.
- Norton MC, et al. Greater risk of dementia when spouse has dementia? The Cache County study. *Journal of the American Geriatrics Society*. 2010; 58:895–900. [PubMed: 20722820]
- O'Donovan A, et al. Stress appraisals and cellular aging: a key role for anticipatory threat in the relationship between psychological stress and telomere length. *Brain, Behavior, and Immunity*. 2012; 26:573–579.
- Oken BS, Fonareva I, Wahbeh H. Stress-related cognitive dysfunction in dementia caregivers. *Journal of Geriatric Psychiatry and Neurology*. 2011; 24:191–198. [PubMed: 22228825]
- Palma KA, et al. Emotional memory deficit and its psychophysiological correlate in family caregivers of patients with dementia. *Alzheimer Disease and Associated Disorders*. 2011; 25:262–268. [PubMed: 21285855]
- Roepke SK, et al. Personal mastery is associated with reduced sympathetic arousal in stressed Alzheimer caregivers. *The American Journal of Geriatric Psychiatry*. 2008; 16:310–317. [PubMed: 18378556]
- Roepke SK, et al. Carotid plaque in Alzheimer caregivers and the role of sympathoadrenal arousal. *Psychosomatic Medicine*. 2011a; 73:206–213. [PubMed: 21217096]
- Roepke SK, et al. Effects of Alzheimer caregiving on allostatic load. *Journal of Health Psychology*. 2011b; 16:58–69. [PubMed: 20709885]
- Roepke SK, et al. Relationship between chronic stress and carotid intima-media thickness (IMT) in elderly Alzheimer's disease caregivers. *Stress*. 2011c; 15:121–129. [PubMed: 21790484]
- Rowe MA, McCrae CS, Campbell JM, Benito AP, Cheng J. Sleep pattern differences between older adult dementia caregivers and older adult noncaregivers using objective and subjective measures. *Journal of Clinical Sleep Medicine*. 2008; 4:362–369. [PubMed: 18763429]
- Schoenmakers B, Buntinx F, Delepeleire J. Factors determining the impact of care-giving on caregivers of elderly patients with dementia. A systematic literature review. *Maturitas*. 2010; 66:191–200. [PubMed: 20307942]
- Segerstrom SC, Schipper LJ, Greenberg RN. Caregiving, repetitive thought, and immune response to vaccination in older adults. *Brain, Behavior, and Immunity*. 2008; 22:744–752.
- Thorpe JM, et al. Caregiver psychological distress as a barrier to influenza vaccination among community-dwelling elderly with dementia. *Medical Care*. 2006; 44:713–721. [PubMed: 16862032]
- Tomiyama AJ, et al. Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. *Physiology & Behavior*. 2012; 106:40–45. [PubMed: 22138440]
- Tschanz JT, et al. Caregiver Coping Strategies Predict Cognitive and Functional Decline in Dementia: The Cache County Dementia Progression Study. *Am J Geriatr Psychiatry*.
- Vitaliano PP, Zhang J, Scanlan JM. Is caregiving hazardous to one's physical health? A meta-analysis. *Psychological Bulletin*. 2003; 129:946–972. [PubMed: 14599289]
- Vitaliano PP, et al. Psychophysiological mediators of caregiver stress and differential cognitive decline. *Psychology and Aging*. 2005; 20:402–411. [PubMed: 16248700]
- Vitaliano PP, et al. Depressed mood mediates decline in cognitive processing speed in caregivers. *Gerontologist*. 2009; 49:12–22. [PubMed: 19363000]
- von Kanel R, et al. Exaggerated plasma fibrin formation (D-dimer) in elderly Alzheimer caregivers as compared to noncaregiving controls. *Gerontology*. 2005; 51:7–13. [PubMed: 15591750]
- von Kanel R, et al. Sleep and biomarkers of atherosclerosis in elderly Alzheimer caregivers and controls. *Gerontology*. 2010; 56:41–50. [PubMed: 19955705]

- von Kanel R, et al. Increased Framingham Coronary Heart Disease Risk Score in dementia caregivers relative to non-caregiving controls. *Gerontology*. 2008; 54:131–137. [PubMed: 18204247]
- von Kanel R, et al. Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal study. *Gerontology*. 2012a; 58:354–365. [PubMed: 22133914]
- von Kanel R, et al. Regular physical activity moderates cardiometabolic risk in Alzheimer's caregivers. *Medicine and Science in Sports and Exercise*. 2011; 43:181–189. [PubMed: 20473220]
- von Kanel R, et al. Effect of chronic dementia caregiving and major transitions in the caregiving situation on kidney function: a longitudinal study. *Psychosomatic Medicine*. 2012b; 74:214–220. [PubMed: 22286846]
- von Kanel R, et al. Sleep in spousal Alzheimer caregivers: a longitudinal study with a focus on the effects of major patient transitions on sleep. *Sleep*. 2012c; 35:247–255. [PubMed: 22294815]
- Wahbeh H, Kishiyama SS, Zajdel D, Oken BS. Salivary cortisol awakening response in mild Alzheimer disease, caregivers, and noncaregivers. *Alzheimer Disease and Associated Disorders*. 2008; 22:181–183. [PubMed: 18525292]

Figure 1.
Systematic review search flow diagram

Table 1

Systematic review search strategy

Search Items	
1	caregiver OR carer
2	dementia OR Alzheimer's disease
3	#1 AND #2
4	stress OR health OR biomarker
5	#3 AND #4
6	intervention OR bereavement
7	#5 NOT#6

Note: MEDLINE, PsycINFO, Global Health, EBM reviews Cochrane Database of Controlled Trials and EBM reviews Cochrane Database of Systematic Reviews were searched. The search was limited to publications in English, with duplicates removed. Only studies including dementia caregivers and non-caregiver peers were considered.

Table 2

Studies assessing effects of dementia caregiving on physiologic biomarkers

Ref.	Study design	Samples N; mean age; % female	Main outcome measures	Group differences	Related or modifying variables
Markers of sympathetic nervous system activity					
(Mills et al., 2004)	CC	DCG: n=69; 74 y.o.; 62% 100% PWD spouse CTL: n=37; 68 y.o.; 81%	β_2-adrenergic receptor sensitivity and density	Lower β_2 -adrenergic receptor sensitivity in vulnerable DCGs vs. CTLs, $d = -.62$, or other DCGs, $d = -.66$. Lower β_2 -adrenergic receptor density in vulnerable DCGs vs. other DCGs, $d = -1.36$, and CTLs, $d = -.90$.	Respite amount affected caregiver effect on the biomarkers, by increasing vulnerability of the DCGs using respite less than once a month.
Metabolic and other health-related markers					
(Brummert et al., 2005)	CS	DCG: n=147; 61 y.o.; 75% 47% PWD spouses CTL: n=147; 56 y.o.; 75%	Fasting plasma glucose (FPG), glycosylated hemoglobin concentration (HbA1c); neighborhood characteristics	Overall, DCGs and CTLs were similar on levels of FPG, $d = .09$, and HbA1c, $d = .04$.	Neighborhood characteristics moderated caregiving effect on glucose levels. In better neighborhoods DCGs and CTLs were similar on glucose metabolism; in worse neighborhoods, DCGs had higher FPG, $p < .002$, and HbA1c, $p < .001$, than CTLs.
(Mausbach et al., 2010)	CC	DCG: n=55; 74 y.o.; 69% 100% PWD spouses CTL: n=23; 74 y.o.; 78%	Endothelial function (brachial artery flow-mediated dilation (FMD))	DCGs of PWD with moderate to severe dementia had worse FMD than DCGs of PWD with mild dementia, $d = -.69$, or CTLs, $d = -.60$.	FMD was linked to PWD's dementia severity, $p = .03$, and years of caregiving, $p = .004$, with DCG with over 4 years of caregiving displaying worse FMD than CTLs, $p = .025$.
(Roepke, Mausbach et al., 2011)	CC	DCG: n=87; 74 y.o.; 71% 100% PWD spouses CTL: n=43; 75 y.o.; 61%	Allostatic load index (BP, BMI, HDL cholesterol ratio, HDL cholesterol, plasma NE, and EPI)	DCGs had higher diastolic BP than CTLs, $d = .36$. At a trend level, $p = .076$, DCGs had greater allostatic load scores than CTLs, $d = .38$.	Personal mastery moderated caregiving and allostatic load relationships. In those high on mastery, DCGs had greater allostatic load than CTLs, $p = .003$; but no group difference in those low on mastery.
(Roepke, Chatillion et al., 2011)	CC	DCG: n=111; 74 y.o.; 69% 100% PWD spouses CTL: n=51; 75 y.o.; 69%	BP, carotid artery plaque and plasma catecholamine responses to acute stress	Caregiving status was related to a 2.2 times greater odds for the presence of plaque, $p = .048$ independent of other risk factors of atherosclerosis. Decreased recovery to basal levels of epinephrine post-stress related to the presence of plaque in DCGs, but not CTLs.	Presence of plaque in DCGs was linked to decreased recovery to basal levels of epinephrine after psychological stress.
(von Kanel et al., 2008)	CC	DCG: n=65; 73 y.o.; 72% 100% PWD spouses CTL: n=41; 68 y.o.; 78%	Framingham coronary heart disease (CHD) Risk Score	Higher clinically relevant risk of developing CHD over 10-years in DCGs vs. CTLs, $d = .57$, and higher systolic BP in DCGs vs. CTLs, $d = .84$.	Systolic BP contributed the most to the differences in DCGs and CTLs in average risk score
(von Kanel et al., 2011)	CS	DCG: n=115; 74 y.o.; 70% 100% PWD spouses	Cardiometabolic risk factors; physical activity	Compared to CTLs, DCGs had a trend, $p = .056$ for a greater cardiometabolic risk score, $d = .28$.	Physical activity moderated the relationships between caregiving and cardiometabolic risk. In those with low activity level, higher cardiometabolic risk in DCGs vs. CTLs, $d = .58$; but no

Ref.	Study design	Samples N; mean age; % female	Main outcome measures	Group differences	Related or modifying variables
(von Kanel, Mausbach, Dimsdale et al., 2012)	Long. F/u up to 3 years	CTL: n=54; 74 y.o.; 67% DCG: n=119; 74 y.o.; 70% 100% PWD spouses CTL: n=58; 75 y.o.; 67%	Markers of kidney function (glomerular filtration rate, GFR), and BP	Kidney function was similar between DCGs and CTLs over the study period, $p = .77$. However, 3 months after PWD's nursing home placement, in DCGs with hypertension (high diastolic BP), GFR declined by 8.33 mL/min, $p = .004$.	group differences in those with high activity levels. BP moderated the rate of change in GFR in DCGs with increased sympathetic activation after major transition (e.g. PWD nursing home placement).
Markers of procoagulant activity					
(Aschbacher et al., 2005)	CC	DCG: n=60; 72 y.o.; 63% 100% PWD spouses CTL: n=33; 68 y.o.; 76%	D-dimer (DD) levels and BP; coping	There was a trend, $p = .086$, $\eta^2 = .03$, for DCGs to have greater procoagulability than CTLs.	Coping buffered the impact of stress on pro-coagulant activity. Significant 3-way interaction between problem solving, DCG status, and DD pattern, $p = .004$, with greater DD increases from baseline to speech stressor in DCGs with low problem solving level vs. CTLs. Approach coping related to DD.
(Mausbach, von Kanel et al., 2007)	Long. F/u 5 years	DCG: n=112; 73 y.o.; 68% 100% PWD spouses CTL: n=53; 67 y.o.; 76%	Tissue-type plasminogen activator (t-PA) assay and BP	No baseline difference on t-PA antigen levels between the groups, $p = .88$, but increased t-PA antigen levels over time in DCGs vs. CTLs, $p = .02$. DCGs showed greater t-PA antigen increases over 5 years, $p < .001$, with the rate of increase 3 times greater than that of CTLs.	None reported.
(Mills et al., 2009)* also in Table 3	CC	DCG: n=81; 72 y.o.; 72% 100% PWD spouses CTL: n=41; 67 y.o.; 73%	D-dimer (DD) and interleukin-6 levels; sleep assessed using polysomnography	Male DCGs of PWD with worse dementia had greater DD levels compared to female DCG peers and male DCG of PWD with mild dementia or CTLs, $p = .034$. Male DCGs of PWD with more severe dementia had longer awake after sleep onset than other male DCGs, female DCGs, and CTLs.	Gender, PWD dementia severity, and time awake after sleep onset predicted DD level. Greater coagulation was linked to disturbed sleep in male DCGs, who are vulnerable to increased CVD risk.
(von Kanel, Ancoli-Israel et al., 2010)* Also in Table 4	CS	DCG: n=97; 72 y.o.; 71% 100% PWD spouses CTL: n=48; 68 y.o.; 73%	IL-6, CRP, D-dimer (DD), and Willebrand factor antigen; actigraphy and PSQI for sleep	Greater DD levels in DCGs vs. CTLs, $d = .59$, and a trend, $p = .071$, for greater IL-6 levels, $d = .27$, in DCGs vs. CTLs; Lower sleep percent and quality than in DCGs vs. CTLs, with stronger relationships in DCGs between sleep deficits and IL-6, and CRP levels.	Levels of DD and von Willebrand factor antigen were negatively related to PSQI sleep quality.

Abbreviations: BMI = body mass index, BP = blood pressure, CHD = Coronary Heart Disease, CRP = C-reactive protein, CTL = control, non-caringiving peers, CVD = cardiovascular disease, DCG = Dementia Caregivers, DD = D-dimer, FMD = flow mediated dilation, F/u = follow-up, IL-6 = interleukin-6, PSQI = Pittsburgh Sleep Quality Index, Ref. = reference.

Notes: Cohen's d estimated using pooled standard deviation. P values are presented when Cohen's d could not be calculated from the available data. Primary objective measures are highlighted in bold font.

Table 3
Studies assessing effects of dementia caregiving on markers of HPA activity, immune function, and cellular aging

Ref.	Study design	Samples N; mean age; % female	Main outcome measures	Group differences	Related or modifying variables
Markers of hypothalamic-pituitary-adrenal (HPA) axis activity					
(Brummert et al., 2008)	CC	DCG: n=42; 70y.o.; 0% Relationship to PWD: not reported CTL: n=32; 66 y.o.; 0%	24-h urine cortisol sample; MAOA genotyping	DCGs with less active MAOA genotype had different cortisol excretion pattern compared to DCGs with more efficient MAOA genotype copy, d = 0.54, and CTLs, p < 0.043.	In males, MAOA-uVNTR genotype moderated the effect of chronic stress on urinary cortisol excretion pattern.
(de Vugt et al., 2005)	CC	DCG: n=57; 60 y.o.; 63% 49 % PWD spouses CTL: n=55; 61 y.o.; 65%	Salivary cortisol (4 samples)	Higher cortisol on morning awakening, d = .70, and a smaller increase in cortisol after awakening, p = .036 in DCGs vs. CTLs. Elevated morning cortisol levels could predispose DCGs, especially those who care for PWD with high levels of behavioral and psychological symptoms of dementia, to negative health consequences.	PWD symptoms moderated caregiver effect on cortisol. DCGs of PWD with more dementia symptoms had greater cortisol level 30 min after awakening than DCGs of PWD with fewer dementia symptoms, p = .017.
(McCallum et al., 2006)	CS	AA DCG n=30; 58 y.o. 100% 16% PWD spouses EA DCG n=24; 68 y.o.; 100% 75% PWD spouses CTL n=63; 62 y.o.; 100%	Salivary cortisol (5 times samples during 2 days).	Caregiver status did not affect cortisol levels.	Age, p = .023, and ethnicity, p = .034, predicted cortisol slope: AA had flatter slope than EA. Diurnal cortisol patterns were related to stress-related growth. Cultural and ethnic background might affect cortisol function.
(Tomiyama et al., 2012)	CC	DCG: n=14; age: 51–79, 100% 100 % PWD partners CTL: n=9; age: 51–79, 100%	Daily pattern and acute salivary cortisol, overnight urinary cortisol, telomere length	Caregiver status was not a moderator for any variable.	Greater cortisol responses to acute stress, r = -.46, urinary cortisol levels, r = -.64, and flatter daytime cortisol slopes, r = -.40, related to shorter telomere length.
(Wahbeh et al., 2008)	CC	DCG: n=15; 70 y.o.; 60% Relationship to PWD: not reported CTL: n=15; 75y.o.; 67% PWD: n=19; 75 y.o.; 58%	Salivary cortisol (5 samples during a day)	Increased cortisol levels between awakening and 30 min after awakening in DCGs and PWDs vs. CTLs, p < .0001. Cortisol increased between awakening and 30 min after in DCGs, p < .03, and PWD, p < .01, but not CTLs, p > .27.	DCGs with greater cortisol levels 30 min after awakening showed a trend toward higher stress levels, p = .10.
Markers of immune function					
(Gouin et al., 2012)	CS	DCG: n=53; 64 y.o.; 79% Relationship to PWD: not reported CTL: n=77; 66 y.o.; 84%	C-reactive protein (CRP) and interleukin-6 (IL-6); daily stressors	CTLs and DCGs did not differ in IL-6 levels, p = .80, but DCGs had higher CRP values than CTLs, p = .03, d = .39. Compared to CTLs, DCGs were more likely to report multiple stressors in the previous 24 hours, p = .006.	Daily stressors related to IL-6, p = .07, and CRP levels, p = .04. Frequency of daily stressors in previous 24 hours partially mediated the caregiving and CRP relationship.
(Kiecolt-Glaser et al., 2003)	Long. F/u 6 years	DCG: n=119; age: 55–89 100% PWD spouses CTL: n=106; age: 55–89 71 % female for whole sample	Plasma IL-6 level twice a year for 6 years	DCGs had four times the rate of increase in IL-6 of CTLs' rate, p = 0.02. In former DCGs, the mean annual change in IL-6 was similar to that of current DCGs even after several years after PWD's death.	None reported.

Ref.	Study design	Samples N; mean age; % female	Main outcome measures	Group differences	Related or modifying variables
(Segerstrom et al., 2008)	Long, F/u 5 years	DCG: n=14; 73 y.o.; 50% 100 % PWD spouses CTL: n=30; 75 y.o.; 60%	Post-influenza vaccine antibody, interleukin-6 (IL-6), trait repetitive thought	Though, pre-vaccination, DCGs had a trend for higher IL-6 levels compared to CTLs, $p > .05$, $\eta^2 = .28$, after vaccination DCGs IL-6 levels were significantly higher than those of CTLs, $p < .05$, $\eta^2 = .44$.	For DCGs, negative repetitive thought related to depression and lower antibody titers. Neutral repetitive thought predicted less depression but higher antibody titers and post-vaccination IL-6 levels.
(von Kanel, Mills et al., 2012)	Long, F/u 3 years	DCG: n=118; 74 y.o.; 70% 100% PWD spouses CTL: n=51; 74 y.o.; 65%	Markers of inflammation, cellular adhesion, endothelial function, and hemostasis	Compared to CTLs, DCGs had 16 % greater TNF- α levels over time, $p = .048$. Cessation of DCG duties resulted in a decreased DCG inflammatory state: three months after PWD's death, DCGs had lower CRP, $p = .003$, and sICAM-1 levels, $p = .008$, compared to acting DGCs.	Caregiving duration (15 years vs. <15 years) related to CRP levels, $p = .040$, with CRP levels for long-term DCGs twofold higher than those of novice DCGs and CTLs.
(von Kanel, Mausbach, Ancoli-Israel et al., 2012) *	Long, F/u up to 3 years	DCG: n=109; 74 y.o.; 70% 100 % PWD spouses CTL: n=48; 75 y.o.; 63%	IL-6 and TNF-alpha; actigraphy (three 24-h periods) for sleep quality	DCGs and CTLs had similar sleep trajectories. PWD's placement did not affect DCG sleep but PWD's death was linked to increased DCG WASO and daytime sleep, as well as to decreased nighttime sleep %.	TNF- α moderated the relationships between caregiving and WASO, $p = .049$, and sleep percent, $p = .025$, with TNF- α levels linked to sleep quality in DCGs.
Markers of cellular aging					
(Damjanovic et al., 2007)	CC	DCG: n=41; 65 y.o.; 73% 63% PWD spouses CTL: n=41; 65 y.o.; 73%	Telomere length and telomerase activity, cytokines	Lower T cell proliferation, $d = -2.53$, but greater production of TNF- α and IL-10 in response to stimulations in vitro in DCGs vs. CTLs, $p < .05$. DCGs had shorter PBMC telomeres, $d = -2.0$, and DCGs had greater basal telomerase activity than CTLs, $p < .0001$, indicating failed attempts of cells to compensate for excessive telomere loss.	None reported.
(Epel et al., 2010)	CC	DCG: n=22; age: 51–75, 100% PWD partners CTL: n=21; age: 51–75; 100%	Telomerase activity; salivary cortisol, flow cytometry	DCGs had marginally lower baseline levels of telomerase activity than CTLs, $p = .06$, but significantly lower telomerase activity than CTLs across time, $p < .01$.	After acute stressor, telomerase activity related to cortisol changes in response to stressor and to threat perception.
(Kiecolt-Glaser et al., 2011)	CS	DCG: n=58; 70 y.o.; 71% Relationship to PWD: not reported CTL: n=74; 70 y.o.; 73%	Serum IL-6 and TNF-α levels and telomere length; child abuse and neglect	Shorter telomere length, $p = .04$, $d = .48$ and marginally higher TNF- α levels, $p = .08$, in DCGs vs. CTLs. Among those reporting child abuse, TNF- α level effect was magnified for DCGs compared to CTLs.	Caregiving status by child abuse interaction, $p = .05$, with higher TNF- α levels in abused DCGs vs. non-abused DCGs, $p = .009$, or abused and non-abused CTLs, $p = .01$
(O'Donovan et al., 2012)	CC	DCG: n=27; age: 51–79; 100% Relationship to PWD: not reported CTL: n=23; age: 51–79, 100%	BMI and telomere length; threat and challenge appraisal	No main caregiving effect on telomere length, $p = .23$.	Threat sensitivity mediated the chronic stress and cellular aging relationship with caregiving effect on telomere length through anticipatory threat appraisals associated with telomere lengths only in DCGs, $p = .03$.

Abbreviations: AA = African American, BMI = body mass index, BP = blood pressure, CRP = C-reactive protein, CTL = control, non-caregiving peers, DCG =Dementia Caregivers, EA = European American, F/u = follow-up, MAOA = monoamine oxidase A, MCI = mild cognitive impairment, NPI = Neuropsychiatric inventory, PBMC = peripheral blood mononuclear cell, Ref. = reference, SES = socioeconomic status, sICAM = soluble intercellular adhesion molecule, TNF- α = tumor necrosis factor- α .

Notes: Cohen's d estimated using pooled standard deviation. P values are presented when Cohen's d could not be calculated from the available data. Primary objective measures are highlighted in bold font.

Table 4

Studies assessing objective sleep measures in dementia caregivers

Ref.	Study design	Samples N; mean age; % female	Main outcome measures	Group differences	Related or modifying variables
(Castro et al., 2009)	CC	DCG: n=9; 63 y.o.; 100% 67% PWD spouses CTL: n=34; 62 y.o.; 100%	Ambulatory PSG (3 nights), PWD: actigraphy, PSQI and sleep diaries	Longer PSQI sleep latency, $d = 1.05$ and more sleep disturbances, $d = .72$, in DCGs than CTLs. Similar PSG sleep latency, $d = .27$, and WASO, $d = .30$ between the groups.	PWD sleep patterns affected DCG sleep.
(Fonareva et al., 2011)	CC	DCG: n=20; 65 y.o.; 90% 70% PWD spouses CTL: n=20; 67 y.o.; 90%	Ambulatory PSG (1 night), salivary cortisol, CRP, and salivary cortisol	Longer sleep onset latency, $d = .49$, more sleep time in stage 1, $d = .56$, and less time in stage R, $d = -.64$ in DCGs than CTLs.	Sleep quality related to CRP and waking cortisol. Group effects: CRP, $d = .44$, cortisol, $d = .61$.
(McKibbin et al., 2005)	CS	DCG: n=73; 72 y.o.; 71% 100% PWD spouses CTL: n=40; 68 y.o.; 71%	In-home PSG (1 night) and PSQI for sleep quality assessment	Older DCGs for PWD with moderate/severe dementia slept 51 min less than older CTLs and reported more sleep problems on PSQI, $p's < .05$.	Age predicted sleep efficiency, SWS, and Stage 1 sleep.
(Mills et al., 2009)* Also included in Table 2	CS	DCG: n=81; 72 y.o.; 72% 100% PWD spouses CTL: n=41; 67 y.o.; 73%	In-home PSG (1 night); biomarkers (D-dimer levels) collected in the morning	Male DCGs of PWD with more severe dementia had greater time awake after sleep onset (132 min) compared to male DCG of PWD with mild dementia (89 min), female DCGs of PWD with severe dementia (77 min) and mild dementia (98 min), and CTLs (76 min).	Gender $\times$ PWD severity interaction, $p < .02$. Time awake after sleep onset independently predicted D-dimer levels, $p = .046$.
(Rowe et al., 2008)	Corr. post-hoc review	DCG: n=31; 71 y.o.; 74% Relationship to PWD: not reported CTL: n=102; 73 y.o.; 64%	Wrist actigraphy (7 days), subjective sleep assessed with a sleep diary	Longer sleep latency, $d = .69$, less sleep, $d = -.60$, and lower sleep efficiency, $d = -.126$, in DCGs, as well as greater night-to-night sleep variability compared to CTLs.	Depressive symptoms predicted self-reported sleep problems (TST, sleep latency, and WASO).
(von Kanel, Ancoli-Israel et al., 2010)* Also included in Table 2	CS	DCG: n=97; 72 y.o.; 71% 100% PWD spouses CTL: n=48; 68 y.o.; 73%	Wrist actigraphy (3 nights) and self-reported sleep quality with PSQI, IL-6, CRP, D-dimer, and Willebrand factor antigen	Lower sleep percent, $d = -.28$, and greater WASO time, $d = .39$, in DCGs when measured objectively. Subjectively, poorer PSQI sleep quality, $d = .43$ in DCGs. Stronger relationships between sleep and IL-6 and CRP levels in DCGs.	PSQI sleep quality related to DD and von Willebrand factor antigen.
(von Kanel, Mautsch, Ancoli-Israel et al., 2012)* Also included in Table 2	Long. F/u 3 years	DCG: n=109; 74 y.o.; 70% 100% PWD spouses CTL: n=48; 75 y.o.; 63%	Wrist actigraphy (3 24-h periods) and perceived sleep quality with PSQI; IL-6 and TNF-alpha	At baseline lower PSQI sleep quality in DCGs, $d = .72$ but groups similar on baseline objective sleep measures and sleep trajectories over time. No effect on sleep of PWD placement to a care facility, but PWD death linked to increasing DCG WASO by 23 min and daytime sleep by 29 min, and decreasing nighttime sleep by 3%.	Age, gender, role overload, depressive symptoms, and pro-inflammatory cytokines moderated relationship between caregiving and transition to poor sleep

Abbreviations: CC = case-control, Corr. = correlational, CRP = C-reactive protein, CS = cross-sectional, CTL = controls, non-caregiving peers, DCG = dementia caregivers, DD = D-dimer, F/u = follow-up, IL-6 = interleukin-6, Long. = longitudinal, PSG = polysomnography, PSQI = Pittsburgh Sleep Quality Inventory, PWD = person with dementia, Ref. = reference, SWS = slow wave sleep, TST = total sleep time, WASO = wake after sleep onset.

Notes: Cohen's d estimated using pooled standard deviation. P values are presented when Cohen's d could not be calculated from the available data. Objective sleep measures are highlighted in bold font.

Table 5

Studies assessing effects of dementia caregiving on cognitive function

Ref.	Study design	Samples N; mean age; % female	Main outcome measures	Group differences	Related or modifying variables
(Caswell et al., 2003)	CC	DCG: n=44; 74 y.o.; 52% 100% PWD spouses CTL: n=66; 71 y.o.; 68%	WAIS-R Digit Symbol test (information processing speed, attention, and concentration)	DCGs deficits on complex attention and processing speed, $d = -.62$. Caregiver status predicted DST score, $\Delta R^2 = .03$, $p < .035$.	Digit Symbol scores were also affected by age and education.
(de Vugt et al., 2006)	Long. F/u 1 year	DCG: n=54; 68 y.o.; 59% 100% PWD spouses CTL: n=108; 68 y.o.; 59%	MMSE (global cognitive functioning), delayed recall AVLT (memory retrieval), LDCT (processing speed), Stroop (cognitive flexibility), Granger Intelligence Test	DCGs performed worse on global cognitive function, $d = -.42$, memory delayed recall, $d = -.49$, and processing speed, $d = -.77$, but groups were similar on cognitive flexibility, $d = .33$.	Verbal memory task performance was related to DCG subjective competence and PWD hyperactivity.
(Norton et al., 2010)	PB F/u: up to 12.6 years	PWD spouse: n=229; 76 y.o. Non-PWD spouse: n=2213; 74 y.o. Gender distribution not reported.	MMSE , IQCODE neurological exam , 1-hour battery of neuropsychological tests ; dementia diagnosis reached by psychiatric examination and confirmed by a panel of experts	Greater risk for developing dementia in PWD spouses ($HRR = 6.4$). The risk was greater for male rather than female PWD spouses ($HRR = 11.9$ vs. 3.7).	Gender emerged as a moderating factor. Risk of developing dementia was linked to older age, lower SES, and presence of APOE $\epsilon 4$ allele.
(Oken et al., 2011)	CC	DCG: n=31; 65 y.o.; 81% Relationships to PWD: not reported CTL: n=25; 67 y.o.; 88%.	ANT (attention task), Stroop (executive function task), word list (verbal memory task); sleep quality assessed by PSQI	DCG performed worse than on ANT, $d = .60$, and Stroop, $d = .38$, but groups were similar on the word memory test, $d = -.16$.	Sleep quality mediated caregiver effect on cognitive performance.
(Palma et al., 2011)	CS	DCG: n=14; age range: 66–74; 50% Relationship to PWD: not reported CTL young: n=19; age range: 35–49; 80% CTL old: n=24, age range 61–82; 83%	Memory task : tested delayed recall of emotionally arousing or neutral story, salivary cortisol	Unlike older CTLs, DCGs did not benefit from emotionally arousing material, with similar percentage of correct answers for emotional and neutral material, $p > .05$. Lower percentage of correct answers overall in DCGs compared to older CTL, $p = .011$.	Nighttime cortisol levels, which were higher in DCG, predicted memory performance.
(Vitaliano et al., 2005)	Long. F/u: 2 years	DCG: n=96; 72 y.o.; 60% 100 PWD % spouses CTL: n=95; 71 y.o.; 62%	Vocabulary and abstraction subscales ; glucose, insulin level, and BP; hostility	Groups similar at baseline, but 2 years later, DCGs but not CTLs had a 1-point decline on the vocabulary test, $p < .05$.	Hostile attribution and metabolic risk mediated DCG cognitive decline.
(Vitaliano et al., 2009)	Long. F/u: 2 years	DCG: n=122; 72 y.o.; 62% 100 PWD % spouses CTL: n=117; 70y.o.; 64%	Digit Symbol Test (processing, psychomotor speed, attention, concentration).	After 2 years (and at each time point) DCGs had lower DST score, $d = .38$. Over time, DCGs experienced a more rapid decline in cognitive performance (at least 4.5 times faster) than CTLs.	Baseline depression predicted and mediated DST decline in both groups.

Abbreviations: ANT = Attention Network Task, AVLT = Auditory Verbal Learning Test, BP = blood pressure, DCG = dementia caregivers, DST = Digit Symbol Test, CC = case-control, CS = cross-sectional, CTL = controls, non-caregiving peers, F/u = follow-up, HRR = Hazard Rate Ratio, IQCODE = Informant Questionnaire for Cognitive Disorder in Elderly, LDCT = Letter Digit Coding Test, Long. = longitudinal, MMSE = Mini-Mental State Exam, PB = population based, Ref. = reference, SES = socioeconomic status, Stroop = Stroop Color-Word Test, TICS = Telephone Interview of Cognitive Status, WAIS-R = Wechsler Adult Intelligence Scale-Revised.

Notes: Cohen's d estimated using pooled standard deviation. P values are presented when Cohen's d could not be calculated from the available data. Cognitive measures are highlighted in bold font.