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A systematic review of the psychobiological burden of informal caregiving for patients with dementia: Focus on cognitive and biological markers of chronic stress

For submission to *Neuroscience & Biobehavioral Reviews*

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Graphical abstract

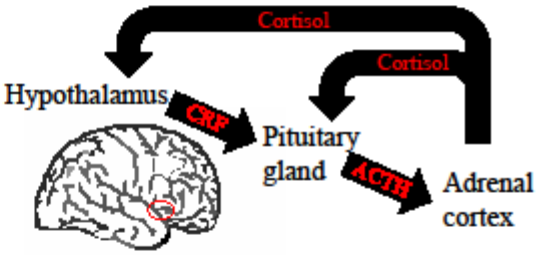
Context

Dementia caregiving stress

Impact

Impaired attention & executive function

Dysregulated HPA axis



Intervention

Stress reduction: Improved cognition

Research Highlights

- Much research has examined biomarkers of chronic stress in dementia caregivers
- Cortisol was increased in dementia caregivers in most studies examining cortisol
- Dementia caregivers displayed poorer attention and executive function performance
- Interventions to reduce stress in caregivers may improve cognition
- Risk of bias was generally low to moderate

Abstract

As the physiological impact of chronic stress is difficult to study in humans, naturalistic stressors are invaluable sources of information in this area. This review systematically evaluates the research literature examining biomarkers of chronic stress, including neurocognition, in informal dementia caregivers.

We identified 151 papers for inclusion in the final review, including papers examining differences between caregivers and controls as well as interventions aimed at counteracting the biological burden of chronic caregiving stress.

Results indicate that cortisol was increased in caregivers in a majority of studies examining this biomarker. There was mixed evidence for differences in epinephrine, norepinephrine and other cardiovascular markers. There was a high level of heterogeneity in immune system measures. Caregivers performed more poorly on attention and executive functioning tests. There was mixed evidence for memory performance. Interventions to reduce stress improved cognition but had mixed effects on cortisol. Risk of bias was generally low to moderate. Given the rising need for family caregivers worldwide, the implications of these findings can no longer be neglected.

Keywords: Stress, caregiver, dementia, cortisol, immune system, cardiovascular, epinephrine, norepinephrine, cognition, attention, memory, biomarker

Introduction

The role of an informal dementia caregiver (i.e. a person providing care to a person with dementia, who is not providing this care in a professional capacity) is a potential source of

substantial psychosocial stress. Patients with dementia may depend increasingly upon informal caregivers, typically close family members, to help them with activities of daily living, as well as displaying challenging behaviours and facing safety issues. In addition to heightened stress, family dementia caregivers show increased levels of anxiety and depression (Baumgarten et al., 1994; Mahoney et al., 2005). Although many informal family caregivers display resilience in the face of their relatives' illness, there is a clear mental health risk within this group. The social impact of this care should not be underestimated; the worldwide economic cost of dementia has been estimated at US$818 billion, and it is predicted that this figure will increase to $2 trillion by 2030 (Prince et al., 2015). Within this context, family caregiving saves the exchequer spending on care provision. The results of research on the chronic stress of caring for people with dementia can be used to provide targeted interventions for attenuating the impact of stress in this group, and potentially in other groups exposed to chronic stressors.

Although there has been much research on the biological and psychological markers that accompany the acute stress response (Allen et al., 2014; Dickerson and Kemeny, 2004), it is unethical to experimentally expose humans to chronic stress. As a result, naturalistic chronic stressors such as dementia caregiving are a useful means for examining the impact of chronic stress on human physiology. A number of such models have been examined, such as unemployment (Dettenborn et al., 2010; Gallagher et al., 2016; Ockenfels et al., 1995), or the ongoing effects of childhood abuse (Carpenter et al., 2009; Penza et al., 2003). Compared to other forms of caregiving, caregiving for a family member with dementia may be a particularly stressful experience (Clipp and George, 1993; Kim and Schulz, 2008). Estimates of median survival time for dementia patients vary between 3.3 years and 11.7 years (Todd et al., 2013), and so dementia caregiving represents a chronic source of stress.

Biomarker research may provide us with a greater understanding of mechanisms through which psychological stress may impact upon long-term health outcomes. For instance,

increases in blood pressure may act to increase the risk of cardiovascular illness (MacMahon et al., 1990) and compromised immune system functioning can impair resistance or response to infectious diseases such as influenza (Godbout and Glaser, 2006). Given that ageing and chronic stress can have similar effects on the brain (Prenderville et al., 2015), the impact of caregiving stress may be compounded where caregivers for elderly relatives are themselves senior citizens. However, this also raises the methodological caveat that the search for biomarkers of caregiver stress should take into account the age of the caregiver, as well the nature of impairment and changes in caregiving intensity (Lovell and Wetherell, 2011).

The key aim of this paper is to describe the results of a systematic review of the literature examining the biological and psychological burden of the chronic stress of dementia caregiving. We also review research looking at interventions to reduce the impact of chronic stress in caregivers, where biomarkers are examined as an outcome. We appraise the research quality of relevant research and identify potential future directions for research in this area.

1. Methods

This systematic review was pre-registered at PROSPERO. ID: PROSPERO 2015:CRD42015020828. The date of registration was 28th May 2015. This is available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020828

2.1. Literature search

The databases Cinahl, PsycINFO, Pubmed, ScienceDirect, Scopus and Web of Knowledge were used as electronic search engines for the systematic review.

The search terms included were: "caregiver" AND "dementia" AND "stress" OR "allostatic load" OR "biomarkers" OR "biological marker" OR "cortisol" OR "cytokine" OR "heart rate" OR "gastrointestinal" OR "interleukin" OR "c-reactive protein" OR "catecholamines" OR "adrenaline" OR "noradrenaline" OR "epinephrine" OR "norepinephrine" OR "pH" OR "amylase" OR "vasopressin" OR "DHEA" OR "DHEA-S" OR "lymphocyte" OR "T-cell" OR "B-cell" OR "monocyte" OR "neutrophil" OR "basophil" OR "granulocyte" OR "macrophage" OR "nuclear factor kappa B" OR "immunoglobulin" OR "heart rate variability" OR "BDNF" OR "d-dimer" OR "tryptophan" OR "kynurenine" OR "blood pressure".

2.2. Exclusion criteria

Studies were excluded if they were not written in English (and a translation was not available), if they did not report original research, if they did not employ a quantitative design, if they did not assess any biomarkers or if they did not assess informal caregivers (i.e. those caring in a non-professional capacity) for patients with dementia. Study review and selection was completed by two reviewers. See Figure 1 for flowchart of study exclusion/inclusion.

2.3. Data Extraction

Two reviewers extracted data on study design, control group, length of follow up, region and time period of study, outcome definitions, interventions, compliance with the intervention, data source, sample size, attrition rate, treatment of missing values, confounders considered, patient's dementia diagnosis, inclusion/exclusion criteria for study participants and participant age, gender, ethnicity, and relation to care recipient.

2.4. Study evaluation

Quality was assessed via a tool based on McDonald et al. (2005), but adapted for the context of dementia caregiving. This quality assessment tool assessed six types of bias: 1. selection (sample selection, rationale for control group and length of assessment, and provision of inclusion/exclusion criteria), 2. Exposure (hours of caring per week, overall duration of caring and assistance with activities of daily living), 3. outcome (description of biomarker assessment), 4.confounding (number of potential confounding factors controlled for), 5. analytic (adequately explanation of statistical methods, application of correction for multiple comparisons where appropriate and sample size adequacy), 6. attrition (rate of attrition and explanation for attrition).

For each article, the six types of bias were classified as low, moderate or high (see Supplementary Table 1 for quality assessment form with detailed description). Furthermore, overall study bias was classified as low, low-moderate, moderate, moderate-high or high, based on an arithmetic mean of bias from the six types of bias. The second reviewer verified the quality assessment of the first reviewer.

2. Results

Of the 8,697 papers initially identified, a total of 151 studies were included in the systematic review (see Figure 1 for inclusion flowchart). This included 133 studies examining the impact of dementia caregiving on stress biomarkers and 18 papers examining the impact of interventions to reduce stress in carers.

3.1. Impact of dementia caregiving on biomarkers of stress

3.1.1. Dementia caregiving and cortisol

Thirty one non-interventional studies examined cortisol levels in dementia caregivers (See Table 1). Of these, twenty-six examined salivary cortisol, three examined plasma cortisol, three examined urinary cortisol, and one looked at hair cortisol (with some studies examining cortisol from multiple sources).

Heightened cortisol was observed in caregivers in sixteen studies (not including studies that focused on factors moderating cortisol output). Of these, seven studies showed increased salivary cortisol when measured at various timepoints throughout the day (Bauer et al., 2000; Da Roza Davis and Cowen, 2001; Davis et al., 2004; Gallagher-Thompson et al., 2006; Palma et al., 2011; Tarrier et al., 2002; Vedhara et al., 1999). In particular, there was evidence from four other studies of increased salivary cortisol at awakening (de Vugt et al., 2005; Fonareva et al., 2011; Oken et al., 2011; Wahbeh et al., 2008) although both an attenuated cortisol awakening response (de Vugt et al., 2005) and Wahbeh et al. (2008) found a clear cortisol awakening response in caregivers at 30 minutes, but not in a non-caregiver control group. Increased cumulative stress load, as indicated from hair cortisol measures, has been reported (Stalder et al., 2014) as has an increase in overnight urinary cortisol (Clark et al., 2007). In terms of response to an acute stressor, both increased saliva cortisol reactivity (Aschbacher et al., 2013) and increased plasma cortisol have been documented (Cacioppo et al., 2000).

The effect of caregiving on cortisol is not always apparent and studies have also found that plasma morning cortisol is unchanged (Irwin et al., 1997; Mills et al., 1997), that there was no difference in salivary cortisol at various timepoints throughout the day or in 12-hour urinary cortisol (Tomiyama et al., 2012) and that there were no differences in plasma cortisol change in response to an acute stressor (Malarkey et al., 1996).

Hypofunction of the HPA axis has also been reported including a reduction in salivary cortisol measured at various timepoints over the day (Jeckel et al., 2010). Deviations from the normal profile despite similar peak levels in caregivers include an earlier onset of salivary cortisol reactivity in response to acute stress (Epel et al., 2010). One study indicated an increased ratio of salivary cortisol to dehydroepiandrosterone (DHEA), which has neuroprotective and antiglucocorticoid effects, suggesting an imbalance in HPA axis activity (Correa et al., 2015). Similarly, another study indicated an increase in salivary dehydroepiandrosterone sulfate (DHEA-S) to cortisol (Jeckel et al., 2010).

A number of moderating factors were observed: age and ethnicity (McCallum et al., 2006; Wilcox et al., 2005) as well as cultural values (Holland et al., 2010), psychological factors: coping style (Merritt and McCallum, 2013; Merritt et al., 2011) and depressed mood (Leggett et al., 2014), caring circumstances: adult day services (Klein et al., 2014) as well as admission and discharge (Neri et al., 2007), and genotype (Brummett et al., 2008).

In summary, the majority of studies using cortisol as a stress readout have revealed abnormal HPA axis function and most support hyperactivity. These assessments vary in terms of timing, the type of biological sample assessed and whether baseline measures or HPA axis challenges were used. We note that many of the studies reported included multiple time points which is critical given the concerns noted with single time point assessments of cortisol (e.g. Allen et al., 2014). Interestingly, there was evidence of alterations in cumulative stress load, the cortisol

awakening response, the diurnal profile of cortisol secretion and the response to an acute stressor. This type of profile suggests that caregivers are exposed to the damaging effects of elevated cortisol across the day and over sustained periods of time; such elevation is known to be associated with psychopathology, including depression (e.g. Dinan, 2001), and irritable bowel syndrome (e.g. Kennedy et al., 2014).

3.1.2. Dementia caregiving and the immune system

Fifty-four non-interventional studies examined either immune system activation or response in dementia caregivers (See Table 2). Differences between caregivers and non-caregivers have been demonstrated by basal comparisons; caregivers had increased peripheral blood levels of C-reactive protein (Fonareva et al., 2011; Gouin et al., 2012), and a longer duration of care was associated with higher levels (Von Känel et al., 2012c), although other studies did not indicate differences (Vitaliano et al., 2007; Von Känel et al., 2006b). There is mixed evidence concerning whether IL-6 levels differ in caregivers (Fonareva et al., 2011; Gouin et al., 2012; Kiecolt-Glaser et al., 2003; Segerstrom et al., 2008; Von Känel et al., 2006b) and TNF-alpha (Fonareva et al., 2011; Von Känel et al., 2012c). Caregivers had an increased percentage of IL-10^{+}, but no difference for cells expressing IL-2 or IFN-gamma in the cytoplasm of CD-4^{+} and CD-8^{+} lymphocytes (Glaser et al., 2001) or peripheral IL-2 levels (Neri et al., 2007). Caregivers did not have altered IgA secretion (Bristow et al., 2008; Neri et al., 2007) and did not differ in lymphocyte full blood counts (Bauer et al., 2000; Reese et al., 1994). Differences in lymphocyte levels in caregivers were lymphocyte-type specific (Mills et al., 1999) while they did not differ for NK cell counts (Reese et al., 1994), NK cell activity or cytotoxic activity (Irwin et al., 1991; Vitaliano et al., 2001).

There is evidence that the immune response to challenge is altered in caregivers. Caregivers had a reduced IL-1beta response to LPS stimulation, along with slower wound healing

(Kiecolt-Glaser et al., 1995). Caregivers also had reduced leukocyte response to mitogens (Cacioppo et al., 1998), reduced mitogen-induced lymphocyte proliferation, reduced mitogen-induced IL-2 production, and reduced lymphocyte sensitivity to glucocorticoids (Bauer et al., 2000). Although caregivers did not differ in lymphocyte full blood counts, they had lower T-cell proliferation in response to phytohaemagluttinin (PHA) stimulation (Bauer et al., 2000; Reese et al., 1994). Caregivers did not differ in percentage T or B cells, monocytes or NK cells, but following stimulation with anti CD-3 and anti-CD28 Abs had lower T-cell proliferation and heightened production of cytokines (TNF-α and IL-10) (Damjanovic et al., 2007), although another study found increased proliferation of mitogen-stimulated T-cells to glucocorticoid challenge (Jeckel et al., 2010). Caregivers had reduced NK response to rIL-2 or rIFN-gamma (Esterling et al., 1994; Esterling et al., 1996).

In addition to in vitro evidence, caregivers had reduced antibody titre responses to the Fluzone vaccine and a more rapid reduction in peripheral blood leukocytes (PBL) ability to synthesize IL-2 after vaccine stimulation (Glaser et al., 1998), although other research did not indicate differences in antibody titres to influenza vaccine (Segerstrom et al., 2008; Vedhara et al., 1999). In contrast, increased antibody titres to HSV-1, with a reduced t-cell proliferative response to HSV-1 (Glaser and Kiecolt-Glaser, 1997), as well as increased antibody titres to EBV virus capsid antigen IgG have been reported. Caregivers also had reduced IgC titres over six months in response to pneumococcal pneumonia vaccination (Glaser et al., 2000).

There is evidence that immune activity in response to acute psychosocial stress is altered in caregivers: in response to a speech stressor, leukocytes were increased and the density of L-selectin was reduced in caregivers (Adler et al., 2002), and there was evidence of increased reactivity and delayed recovery of P-selectin (Aschbacher et al., 2008). Depression acted as a significant predictor of P-selectin reactivity (Aschbacher et al., 2009). Cell adhesion molecules such as L- and P-selectin may have a significant impact upon the immune system's

preparedness to mount a response to challenge (e.g. Dhabhar et al., 1994). Caregivers showed no differences in chemotaxis to the beta-adrenergic agonist, isoproteronol (ISO), or to stromal cell-derived factor-1 (SDF-1), N-formyl-methionyl-leucyl-phenylalanine (FMLP) but reduced FMLP and SDF-1 chemotaxic responses to an acute psychosocial stressor (Redwine et al., 2004).

Beta(2)-adrenergic receptor sensitivity is important for peripheral blood mononuclear cell (PBMC) trafficking and cytokine production. Caregiving overload, that is, feelings that carers were overloaded by their role, as assessed with the Pearlin Role Overload scale (Pearlin et al., 1990) was negatively associated with beta-adrenergic receptor sensitivity, which was also negatively associated with caregiver mastery (Mausbach et al., 2008; Mausbach et al., 2007b). Beta-adrenergic receptor sensitivity was lower in caregivers classified as more vulnerable due to increased care demands (Mills et al., 2004).

A number of moderating effects on immune system activity have been described, including age (Irwin et al., 1997; Kiecolt-Glaser et al., 1996; Mills et al., 1997), as well as gender (Mills et al., 1997; 2009; Thompson et al., 2004), and males caring for spouse with more severe dementia had increased IL-6 levels compared to females caring for a spouse with more severe dementia (Von Känel et al., 2006a) disease status/medical treatment: oral or transdermal hormone replacement therapy with the majority taking estrogen only or estrogen and progesterone (Aschbacher et al., 2007), cancer history (Vitaliano et al., 1998a) and depression (Castle et al., 1995; Scanlan et al., 2001). A number of psychological factors have been found to moderate the effects of caregiver stress, including childhood abuse (Kiecolt-Glaser et al., 2011), life stress rating (Mills et al., 1997) sleep levels (Von Känel et al., 2010a) and leisure satisfaction –for TNF-alpha, IL-8, IFN-gamma, but not for IL-6 or CRP (Von Känel et al., 2014). In addition to these moderating effects, there was a mediating effect of bodily pain on

CRP levels in caregivers, who also reported higher bodily pain than non-caregivers (Graham et al., 2006).

Given findings that caregivers are prone to more days with infectious illness (Kiecolt-Glaser et al., 1991), a greater understanding of immune system changes in dementia caregivers is warranted. In summary, immune system function has been assessed in a variety of ways, including both directly and indirectly, at baseline and following challenges, and via multiple different methodologies. Piecing together the information from these disparate approaches is challenging, and more consistent assessment strategies would benefit the field. Baseline levels of cytokines and acute phase markers such as IL-6, TNF-alpha and CRP which are most frequently assessed in psychiatric populations, and which yield robust results in such populations (Goldsmith et al., 2016), have infrequently been assessed in caregivers and the results have been mixed. Interestingly, depression is associated with both HPA axis hyperactivity and immune system activation and this has been ascribed to impaired glucocorticoid receptor function (Pariante & Lightman, 2008). Although baseline low grade immune system activation is apparent in some caregiver studies, the evidence for this is mixed; there is clearer evidence that the responsivity of the immune system to challenge may be compromised following caregiver stress. More careful target selection will be required in future studies to get a clearer picture of immune system function in caregivers and these studies will need to take account of factors such as duration of caregiving and caregiver burden scores. Importantly, there are well defined routes through which immune system activation can impact at the level of the CNS and a number of anti-inflammatory strategies to counteract such activation. It is premature based on the current data to conclude this would be beneficial in caregivers. Equally, the possibility of a compromised immune system reactivity needs to be considered.

3.1.3. Dementia caregiving and cardiovascular biomarkers

Forty seven non-interventional studies examined cardiovascular variables in dementia caregivers (see Table 3). Caregivers had higher resting heart rate (HR) (Cacioppo et al., 2000; Jeckel et al., 2010), systolic blood pressure (SBP) (Cacioppo et al., 2000) and diastolic blood pressure (DBP) (Cacioppo et al., 2000; Jeckel et al., 2010), although other studies found no difference for caregivers in SBP or DBP (Malarkey et al., 1996; Redwine et al., 2004). Further research has found heightened mean arterial pressure in caregivers (Malarkey et al., 1996; Mausbach et al., 2007c; Redwine et al., 2004). Although one cross-sectional study suggested that there were comparable age-related increases in SBP and HR (Uchino et al., 1992), another study found that although there was not a significant difference in blood pressure (BP) at baseline, BP readings consistent with borderline hypertension were more common in caregivers over a six-year follow-up (Shaw et al., 1999), and longitudinal increase in DBP was related to increase ADL assistance (Shaw et al., 2003). Hospice care was not associated with changes in BP (Irwin et al., 2013).

D-dimer, a hypercoagulability marker that may also be considered a marker of psychosocial distress (Von Känel and Dimsdale, 2003) has been found to be increased in caregivers (Von Känel et al., 2005; Von Känel et al., 2006b), although not after controlling for anxiety and depression (Aschbacher et al., 2005). Clinical dementia rating of the patient was found to be associated with increased baseline D-dimer and D-dimer reactivity (Aschbacher et al., 2006), and higher negative life events were associated with higher D-dimer (Von Känel et al., 2003). Death or placement of the patient is associated with a drop in D-dimer, but only after 6 months or more (Mausbach et al., 2007a). Caregiver had increased tissue-type plasminogen activator antigen over time (Mausbach et al., 2007c), although this was not observed in another report (Von Känel et al., 2005).

A number of composite measures incorporating cardiovascular factors have been assessed in caregivers. A composite measure of allostatic load (based on BP, BMI , NE, EPI, cholesterol) was increased in caregivers (Roepke et al., 2011b), while a composite measure of metabolic syndrome (based on glycosylated hemoglobin concentration, triglycerides, waist circumference and blood pressure) was significantly associated with the patient's cognitive decline (Brummett et al., 2013). Another study did not find a difference for caregivers in a cardiovascular composite based on MAP, HDL and NK cell activity (Vitaliano et al., 2001). A higher rate of problem behaviours by the patient was associated with an increased procoagulent index, derived from von Wildebrand factor, Plasminogen Activator Inhibitor-1, and D-dimer scores (Von Känel et al., 2010b).

A number of other cardiovascular measures have been examined in caregivers, who have been shown to have a higher low frequency/high frequency (LF/HF) ratio (an index of sympathetic activity) during the first half of sleep (Sakurai et al., 2015). Higher burdens in caregivers were associated with lower levels of heart coherence (Sarabia-Cobo, 2015). Caregivers had shorter cardiac pre-ejection periods (Cacioppo et al., 2000), but did not differ from controls in respiratory sinus arrhythmia (Cacioppo et al., 2000; Malarkey et al., 1996). Number of years caring and severity of dementia were associated with lower hyperemia induced flow-mediated dilation (Mausbach et al., 2012; Mausbach et al., 2010). Carotid plaques were more prevalent in caregivers (Roepke et al., 2011a), although caregiving duration did not predict carotid plaques (Roepke et al., 2012). Soluble intercellular adhesion module-1, a marker for cardiovascular risk, was reduced three months following the death of a spouse with dementia (Von Känel et al., 2012c).

There were a number of moderating factors, including gender, on response to acute stress (Atienza et al., 2001; Thompson et al., 2004), and on a composite measure including BP, lipids, BMI, insulin and glucose (Zhang et al., 2006) as well as on DBP (Mills et al., 2009) and D-

dimer (Mills et al., 2009), though this was not the case for ambulatory HR or BP (Atienza et al., 2001). There was mixed evidence on ethnicity (Knight et al., 2007; Knight and McCallum, 1998; Wilcox et al., 2005). Psychological factors moderating the impact of caregiver stress included higher engagement in pleasant events and reduced perceived activity restriction (Chattillion et al., 2013), closer affective bonds (Uchino et al., 1994), higher coping self-efficacy (Harmell et al., 2011), active coping (Kim et al., 2007) and negative life events (Von Känel et al., 2003). Relationship with the care recipient moderated DBP and HR in the presence of the care recipient (King et al., 2002a). Sleep behaviour was associated with heightened D-dimer (Mausbach et al., 2006), but not with hypertension (Schwartz et al., 2013). Cardiovascular disease (Vitaliano et al., 1998b), and lower levels of physical activity (Von Känel et al., 2011b) also moderated caregiver effects, but not genotype (Kring et al., 2010).

In summary, there is mixed evidence concerning differences between caregivers and non-caregivers in heart rate and systolic/diastolic BP, although mean arterial pressure does appear to be elevated in caregivers. There is evidence that D-dimer is elevated, and this effect appears to be due to anxiety and depression. A number of other cardiovascular indices have been measured but have yet to be replicated; further research into heart rate variability over the course of the day may yield greater insight into whether and in what ways heightened stress in caregivers manifests at a cardiovascular level.

3.1.4. Dementia caregiving, epinephrine and norepinephrine

Seventeen non-interventional articles examined epinephrine/norepinephrine (EPI/NE) levels in dementia caregivers (see Table 4). EPI and NE increased over time in caregivers along with stress (Clark et al., 2007), and duration of care was a predictor of EPI but not NE in caregivers (Ho et al., 2014). Caregivers with high life stress had higher NE (Mills et al., 1997) and caregivers identified as vulnerable had higher EPI than non-vulnerable caregivers (Mills et al.,

1999). However, caregivers did not differ from non-caregivers in EPI or NE in five other studies (Cacioppo et al., 2000; Irwin et al., 1991; Irwin et al., 1997; Malarkey et al., 1996; Redwine et al., 2004).

A speech stressor increased EPI and NE in dementia caregivers (Adler et al., 2002), depression in caregivers predicted NE change in another study (Mausbach et al., 2005), and heightened anxiety and depression were associated with impaired recovery in NE (Aschbacher et al., 2008). ADL levels were associated with increased NE reactivity to a speech stressor (Roepke et al., 2008).

A longer time caregiving was associated with higher NE and EPI in caregivers with lower leisure satisfaction (Chattillion et al., 2012). Increased waking after sleep onset was associated with heightened NE in caregivers (Mausbach et al., 2006).

3.1.5. Dementia caregiving, neurocognition and neurotrophins

Ten articles examined cognitive performance or neurotrophins in dementia caregivers (see Table 5). Three of these (Caswell et al., 2003; Vitaliano et al., 2007; Vitaliano et al., 2009) described poorer performance in caregivers on the digit symbols test, an assessment of speed of information processing and complex attention (Wechsler, 1981). Caregivers performed more poorly at an attention test (Attention Network Test) in another study (Oken et al., 2011) and had poorer executive function, as indicated by Trail Making B (Correa et al., 2015), and by Stroop performance in another (Oken et al., 2011). Working memory performance was worsened in caregivers (as assessed with digit span; Correa et al., 2015). Recall was worsened in caregivers (de Vugt et al., 2006; Palma et al., 2011) but not in another study after controlling for covariates (Correa et al., 2015), while other research found that recall was enhanced for emotive stimuli (Palma et al., 2011). There also was evidence of poorer performance on an

embedded figures tests, and trends for poorer performance on a proofreading test (Burns et al., 2002) and cognitive flexibility (de Vugt et al., 2006).

Findings on neurotrophins were mixed; Correa et al. (2015) observed lower brain-derived neurotrophic factor (BDNF) in dementia caregivers, while Hadjiconstantinou et al. (2001) observed increased nerve growth factor (NGF). Although PET has been used to examine the impact of an intervention within dementia caregivers (see section 3.2 on intervention for caregivers), there has been a lack of brain imaging studies comparing caregivers to non-caregivers.

In summary, the most consistent findings on neurocognitive performance in caregivers are those suggesting poorer attention and executive function; findings on memory performance are more mixed, which may be due to differently valenced stimuli. Although research on neurotropins in caregivers has been mixed, only a very small number of studies have examined this, and further research in this area examining levels of caregiver stress more closely is warranted.

3.1.6. Dementia caregiving and other biomarkers

Dementia caregivers did not differ significantly in BMI (Aschbacher et al., 2007; Bauer et al., 2000; Bauer et al., 2001), or in glucose (Brummet et al., 2005) although they had heightened glucose, insulin and obesity in another study (Vitaliano et al., 2005). Males had higher BMI at baseline and follow-up, and although female caregivers did not have higher BMI they gained more weight between baseline and follow-up (Vitaliano et al., 1996a). Higher hostility was associated with higher glucose (Vitaliano et al., 1996b), and psychological distress was associated with higher glucose and mediated higher insulin at follow-up (Vitaliano et al., 1996c). A higher sense of coherence was associated with reduced glucose levels in males,

although caregiver status did not moderate this effect (Zhang et al., 2001). Caregivers did not differ in glycosylated hemoglobin concentration (Brummet et al., 2005).

Caregivers have been found to have shorter telomere lengths (an index of cell ageing) in peripheral blood mononuclear cells (PBMC) (Kiecolt-Glaser et al., 2011), and caregivers had higher basal telomerase activity in PBMC and T cells (Damjanovic et al., 2007). However, another study did not find an effect on telomere length (Tomiyama et al., 2012). In response to an acute stressor, there was a trend for reduced telomerase activity overall, but similar levels of reactivity (Epel et al., 2010).

Reduced percentage sleep has been observed in caregivers (Von Känel et al., 2010a), although an overall difference in sleep efficiency was not observed between caregivers and non-caregivers (Roepke et al., 2011a; Sakurai et al., 2015). In contrast, caregivers spent more time in sleep stage N1, but more in stage R, indicating less restorative sleep (Fonareva et al., 2011). Males caring for spouses with more severe dementia had more time awake after sleep onset and a trend for poorer sleep efficiency than female caregivers caring for spouses with more severe dementia (Mills et al., 2009). Spousal death in caregivers was associated with increased waking after sleep onset, increased daytime total sleep time and reduced night time percent sleep (Von Känel et al., 2012a).

Female caregivers had lower skin temperature at pre-stress baseline and at post-stressor relaxation compared to males (Thompson et al., 2004). Glomerular filtration rate (a marker of kidney function) did not change in caregivers at follow-up, although it fell disproportionately after placement of spouse in a nursing home (Von Känel et al., 2012b). Caregivers had lower levels of plasma tryptophan (a precursor of serotonin, as well as other neuroactive metabolites along the kynurenine pathway), although this finding was not statistically significant (Da Roza Davis and Cowen, 2001).

Overall, there is some mixed evidence for metabolic syndrome biomarkers in caregivers, such as insulin and obesity, and they may only be heightened where distress is more substantial. Where there is a lack of difference in overall sleep, this may mask differences in sleep quality, and gender may moderate some sleep differences in caregivers. There is mixed evidence on telomere length in caregivers, and although other biomarkers of stress have been examined, further research would be required to establish the reliability of these effects. A summary of differences between caregivers and control participants in these biomarkers is provided in Table 6.

3.2. Impact of dementia caregiving interventions on biomarkers of stress

Eighteen studies have examined the impact of interventions on stress biomarkers (see Table 7). Some of these have examined the effect of meditation or yoga on stress biomarkers: three have examined Kirtan Kriya, which enhanced executive function (Lavretsky et al., 2013) and memory, as well as reducing SBP (Innes et al., 2012) and altering genes bearing NF-κB- and IRF-1-response elements (Black et al., 2013). One study examined yoga & compassion meditation, which reduced cortisol (Danucalov et al., 2013). Another study indicated that transcendental meditation increased response speed (Leach et al., 2015). Mindfulness-based CBT improved attention but did not affect cortisol (Oken et al., 2010). In another study kundalini yoga affected numerous brain regions, assessed with PET (Pomykala et al., 2012).

Cognitive behavioural therapy has also been shown to enhance cognitive performance in caregivers (Mackenzie et al., 2013), although there is mixed evidence on cortisol (Aboulafia-Brakha et al., 2014; Vedhara et al., 2003). CBT enhanced IgG response (Vedhara et al., 2003), although combined psycho-education and CBT showed differing trends at post-intervention and follow-up (Wilkins et al., 1999).

A respite intervention reduced EPI but did not affect NE, BP or HR (Grant et al., 2003). A "coping with caregiving" program corrected dysregulation in cortisol, but only in caregivers living with the care recipient and providing longer hours of care per day (Holland et al., 2011). An eight-week support program led to stable NE in comparison to an increase in the control group (Kim, 2011). A pleasant events program led to a reduction in IL-6 (Moore et al., 2013). A video-based coping skills intervention reduced BP, but did not alter BP or HR reactivity to acute stress (Williams et al., 2010). An exercise intervention reduced BP reactivity to acute stress (King et al., 2002b).

Eight studies employed active control conditions (two psycho-education/information support, one psychological/information support plus community services, two relaxing music, one relaxation, one telephone support, one nutrition education), five employed a waitlist/no-treatment control group, one employed both psycho-education support and respite-only control conditions, while four had no control group.

In summary, the most consistent effects of the numerous interventions for caregivers examined appears to be an improvement in cognition. Other biomarkers, such cortisol and immune system factors have also been examined, but this latter body of evidence is less clear.

3.3. Quality assessment

A large majority of studies were rated as having low, low-moderate or moderate bias overall. With regard to sample selection, it should be noted that a number of longitudinal studies have led to the publication of numerous research articles, describing different biomarkers of stress within an overlapping cohort. Most studies reported their inclusion/exclusion criteria. A majority of studies controlled for at least three confounding variables. A majority also reported the duration of care and/or hours per week spent providing care, although there was some variability in the amount of hours per week spent caregiving (including minimum number of

hours required for inclusion in research), and only a minority of studies indicated levels of ADL assistance provided. With regard to statistical analysis, few papers indicated a power analysis to outline whether the study was well-powered to detect expected effect sizes. A summary of the quality assessment is presented in Table 8.

Discussion

This systematic review summarises available data on a broad range of biological and cognitive markers of stress in informal dementia caregivers. The most consistent finding was that dementia caregiving was generally associated with greater HPA axis activity, as indicated by elevated cortisol levels (see Graphical Abstract). This HPA axis hyperactivity was documented using a variety of methodological approaches in different types of biological samples and was apparent at single time points, in the cortisol awakening response and across the diurnal cycle of cortisol secretion. The impact of sustained HPA axis hyperactivity is well documented and has been implicated in the neurobiology of stress-related disorders such as depression (e.g. Otte et al, 2016). Further work is needed to assess the particular aspects of the caregiver experience that may moderate the biological impact of caregiver stress (e.g. challenging behaviours, duration of caregiving, relationship with care recipient), to determine if it is subgroup specific and to determine the best approach to managing any long-term physiological risks of caregiver stress.

Chronic exposure to stress hormones like cortisol during adulthood and aging can have an impact on brain structures involved in cognition (Lupien et al., 2009). It is unsurprising then that there is good evidence to support a cognitive neurobiology of caregiving associated most robustly with poorer performance on attention tasks and executive function performance, although it should be noted that the size of these effects are relatively modest; computerised

tasks that can measure performance (e.g. accurate measurement of reaction time) will thus be more sensitive to such effects. The observed impact upon cognition suggests that there is a functional consequence of the reported HPA axis hyperactivity; this is concerning, given that caregiving for a person with dementia can involve cognitively challenging tasks. This is also consistent with reports of impaired cognitive performance in other stress related disorders such as depression (e.g. Beck, 2008) and irritable bowel syndrome (Kennedy et al., 2014, 2015).

Interestingly, our systematic analysis also indicates that interventions to reduce stress, including meditation as well as cognitive behavioural therapy, can improve cognitive performance (see Graphical Abstract). Unfortunately, the evidence regarding the impact of these interventions on cortisol levels are mixed and, based on the studies assessed here, it is unclear if the improvement in cognition is consistently linked to a blunting of the excessive HPA axis activity. Although pharmacological options targeting cortisol production are available, we note that this approach has not yet yielded impressive results in disorders such as depression (McAllister-Williams et al., 2016), although the populations under assessment are not always enriched for subjects with evidence of a HPA axis abnormality. In any case, it is premature based on the current analysis and in the absence of experimental validation of cortisol as a state or trait biomarker to advocate such an intervention. In this regard, we note the emerging support for the role of the gut microbiome in regulating HPA axis activity (Dinan & Cryan, 2012) and the recent demonstration that this might be achieved via the use of psychobiotics (Allen et al., in press)

Activation of the immune system is associated with stress and has been linked to the emergence of psychopathology, making the assessment of immune function a logical target (Dantzer et al., 2008). In dementia caregivers however, there was mixed evidence. These disparate findings for the plethora of neuroimmune factors assessed make it difficult to difficult to draw firm and meaningful conclusions. The broad range of variables assessed using multiple

methodologies and without a sustained focus on specific targets likely contributes to this uncertainty. In fact, there was stronger evidence for a reduced immune response to various challenges than a baseline alteration in immune function from the analysis of circulating cytokines with additional reports of enhanced sensitivity to glucocorticoid challenge. The reduced ability to mount an appropriate immune response is an obvious concern in this population (Kiecolt-Glaser et al., 1991).

Although sustained elevations in circulating glucocorticoids might be expected to be immunosuppressive, this caregiver immune profile is at odds with that presented in depression, with evidence of immune system activation *despite* excess cortisol concentrations (c.f. review by Pariante & Lightman, 2008). This illustrates that the timing and duration of HPA axis dysfunction can have diverging physiological manifestations. We should also note that there was also evidence of an enhanced immune response and low grade immune system activation in some caregiver studies. Future studies need to determine if this is specific to any particular subgroup of caregivers.

Taken together, these findings highlight risks to caregivers, as well as potential for intervention. Chronic excessive secretion of cortisol has been linked with numerous health problems, including hypertension and depression (e.g. Chrousos & Gold, 1998; Scott & Dinan, 1998). If the immune system is subjugated in response to challenge, then caregivers may experience greater adverse health events from infection (Kiecolt-Glaser et al., 1991). Caregiving for a person with dementia can involve cognitively challenging tasks (e.g. managing difficult behaviours), so findings of reduced attention and executive function performance are of concern, but evidence that such differences can be attenuated by interventions to manage stress is promising.

Longitudinal studies that track caregivers over time would be an informative approach but relatively few studies of this nature exist; assessment of caregivers as patients' dementia progresses allows researchers to build bio-psychosocial profiles of any accumulating effects of increasingly severe chronic stress. It is worth considering that many dementia caregivers may not approach health services until they have been providing care for some time, and so a baseline measurement may not be feasible unless ageing participants are tracked prior to any manifestation of memory problems in the care recipients, or at least prior to memory problems necessitating the provision of care. Increases in problematic behaviours in care recipients are particularly relevant, as these have been shown to be more predictive of caregiver burden than reductions in cognitive capacity in the care recipient (Bédard et al., 1997). Linking the appearance of these problematic behaviours and the associated increase in caregiver burden to a particular biomarker signature or to the emergence of biological abnormalities would be a major advance.

The majority of studies examining the impact of dementia caregiving stress used non-caregivers as a control group, as opposed to caregivers for patients with a different condition or professional caregivers. There was heterogeneity in the comparison groups used to evaluate the specific impact of the interventions, although the most commonly employed approach was an active control group. Interventional research has indicated that meditation or yoga have the potential to improve cognitive performance in dementia caregivers, although some of these studies have small sample sizes (including a study examining the impact of yoga on brain activity using PET; Pomykala et al., 2012). Mindfulness-based interventions may be useful in targeting traits such as emotional intelligence and anxiety sensitivity, which may impact upon stress reactivity (Choi et al., 2014), although emotional cognition also remains an under-studied aspect of cognition within this area.

Studies in this area comparing dementia caregivers to a control group generally used non-caregivers as a control group. Given previous evidence that dementia caregivers experience greater stress than other informal caregivers, it would be of interest if stress biomarkers also differ in a graded fashion between these groups. It would also be of interest to compare family caregivers to professional caregivers, to understand the impact the stress of a loved one having dementia in addition to caring for them, although caring self-efficacy may be considerably lower in family caregivers who are not familiar with dementia or are still learning how to deal with the challenges of providing care.

For the majority of studies, the mean age of participants was over 60 years of age, and so the compounding interaction between aging and the chronic stress of dementia caregiving needs to be considered. This should also be evaluated against the studies that also included caregivers below this age range. Although the majority of dementia carers are women (Prince et al., 2015), the research examined here was not restricted to females, and has indicated the impact of dementia caregiving on biomarkers of stress (e.g. immune system activity) may be moderated by gender. The moderation of stress biomarkers by characteristics of the caregiver is important, given that a systematic review has suggested that the characteristics of caregivers may be a better predictor of patient institutionalisation than the behavioural and psychological symptoms of dementia (Black and Almeida, 2004).

Risk of bias was generally low to moderate. Strengths of the studies reviewed included the fact that most controlled for potential confounders (e.g. age, gender, income), and the studies were generally transparent about their inclusion/exclusion criteria. However, there were weaknesses as well. Many of the studies did not report effect sizes for observed effects. Although laboratory procedures for processing biomarkers are generally reported, a number of studies analysing a particular analyte have collected samples in a way which could reduce comparability between studies (e.g. salivary cortisol being collected at different times of day,

lack of standardisation in assays). A number of papers report on measures statistically integrating multiple biomarkers to form composite measures of cardiovascular risk or allostatic load. Caution should be used in comparing such measures across studies, given that the score will be affected by the nature and number of biomarkers measured, as well as the method of assessment.

Our key methodological recommendations for future research are thus as follows: (i). further prospective/longitudinal designs to allow for greater understanding of the impact of the chronic stress of caregiving over time, (ii). clear reporting of effect sizes and assay techniques, (iii). better-powered intervention studies with well-defined comparison groups, (iv). the assessment of multiple biomarkers of stress within caregiver studies, to allow for associations between different biomarkers to be studied within individuals, (v). detailed phenotyping of caregivers, including better characterisation of the duration and intensity of caregiving, as well as the numerous other factors that can moderate the impact of dementia caregiving on stress biomarkers.

There are a number of different biological and neurocognitive factors that remain unexplored in dementia caregivers. Despite research interest in cognitive performance in this group, brain imaging techniques have had very limited use in research on dementia caregivers; one study has examined the impact of an intervention for caregivers using PET. Polysomnography, which incorporates EEG has been employed, but only to study sleep architecture as opposed to neurocognitive performance. fMRI could be an informative means of examining the underlying neurocognitive impact of stress in dementia caregivers, and would be less invasive than PET. Given findings that caregivers have poorer performance on tests of attention, it is of interest to determine the impact that the stress of dementia caregiving has on frontal cortex function. Similarly, findings of impaired executive function suggest that the anterior cingulate cortex may be implicated in the impact of caregiver stress upon cognition.

Although research on cognition in dementia caregivers has focused on memory, attention and executive function, there is more scope for examining complex cognition in caregivers. As caregivers frequently make decisions for the people that they care for, and as informal caregivers can often experience financial difficulty, it would thus be of interest to examine decision making in caregivers, such as the use of heuristics in financial decision-making. Problem solving could be examined in greater depth, as problem-focused coping may be a healthier approach to dealing with the challenges of providing care.

The microbiota is a promising future direction for the examination of the psychobiology of caregiver stress, and perhaps of chronic stress more broadly. There is existing evidence that the microbiota is altered in the stress-related gastrointestinal disorder irritable bowel syndrome (Jeffery et al., 2012), which is more prevalent in caregivers of people with chronic illnesses (Remes-Troche et al., 2015). Microbiota analysis which follows caregivers prospectively may establish if chronic stress effects are mediated by the microbiota, or indeed if existing changes in the microbiota may be a risk factor for more pathological effects of chronic stress.

We should not ignore that in addition to being stressful, caregiving can be highly rewarding (Boerner et al., 2004; Tarlow et al., 2004), and the potential negative physiological effects of dementia caregiving can be offset by factors such as high levels of self-efficacy (Harmell et al., 2011). Nevertheless it is clear there is a high potential for a widespread detrimental psychobiological impact of caregiving and all relevant stakeholders in the healthcare process need to be cognisant of this for informed management strategies. Further research in this area should help us to better understand what protective factors and targeted interventions can minimise the impact of stress in caregivers for people with dementia, who play a vital role within our society.

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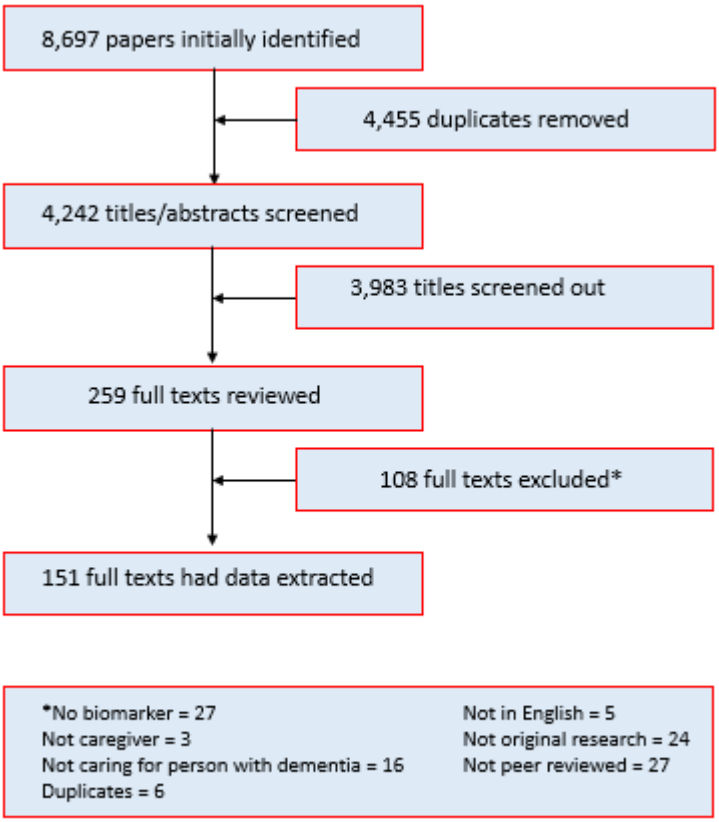

Figure 1: Flow chart of study literature search with reasons for exclusion

Table 1: Summary of studies examining effects of family dementia caregiving on HPA axis activity

Article	Sample size	Participant age, gender & ethnicity	Relation to care recipient	Level of care provided	Biomarkers examined	Findings
Aschbacher et al. (2013)	-CG: N = 25 -Non-CG: N = 23	Mean age: 63, range = 51-79 All female 43 Caucasian, 4 Asian/Pacific Islander, 1 African-American	-	Mean duration = 4.7 years, range = 8 months - 11.42 years	Salivary cortisol	CG: ↑ perceived stress associated with greater anticipatory and peak cortisol reactivity to acute stressor. Non-CG: perceived stress: not associated with peak or anticipatory cortisol.
Bauer et al. (2000)	-CG: N = 49	Mean age = 72, SD = 7.7 F = 24, M = 25 All Caucasian	All spouses	-	Salivary cortisol	Elderly CG: ↑ distress and ↑ salivary cortisol
Brummet et al. (2008)	-CG: N = 42 -Non-CG: N = 32	- CG: Mean age = 70.1, SD = 13.6 80.9% Caucasian, 19.1% African-American	-	-	Urinary cortisol	CG (but not non-CG) with less active MAOA-uVNTR genotype did not show enhanced cortisol

		-Non-CG: Mean age = 66.1, SD = 14.1 78.1% Caucasian, 21.9% African-American All male				output at daytime compared to overnight
Cacioppo et al. (2000)	-CG: N = 27 -Non-CG: N = 37	Mean age = 67.17, SEM = 1.03 83% White, 17% Black All female	All spouses	Mean level = at least 5 hours/week	Plasma cortisol, ACTH	CG: higher plasma ACTH. CG showed larger increase in cortisol in response to stress
Clark, et al. (2007)	At Yr 1: New CG: N = 80 -Veteran CG: N = 120 -Non-CG: N = 60.	-New CG: Mean age = 73.9, SD = 7.1 62.5% female -Veteran CG: Mean age = 74.2, SD = 7.4 65.8% female -Non-CG: 71.9, SD = 7.7 68.2% female	All spouses	-New CG: Mean duration = 5.4 months, SD = 3. -Veteran CG: Mean = 39.7 months, SD = 17.9	Urinary cortisol, EPI NE serum DHEA-S (primary mediators)	Primary mediators significantly associated with stress- ↑ with time for CG but not non-CG

Correa et al. (2015)	-CG: N = 17 -Non-CG: N = 18	-CG: Mean age: 64.83, SEM = 3.64 F = 13, M = 5 -Non-CG: Mean age = 58.29, SEM = 3.16 F = 14, M = 3 -	-	Duration: at least one year Level: at least 8 hours per day	Saliva cortisol and DHEA	CG: ↑ cortisol/DHEA ratio
Da Roza Davis et al. (2001)	-CG: N = 30 -Non-CG: N = 28	-CG: Mean age = 68.8, range = 30-75 years F = 18, M = 12 -Non-CG: Mean age = 68.1, range = 35-84 years F = 17, M = 11 -	-	-	Saliva cortisol (8.00, 12.00, 16.00, 22.00),	Higher cortisol in CG (at 12.00 and 22.00)

Davis et al. (2004)	-CG: N = 30	Mean age = 76.9, SD = 6.9 All female 76.7% Caucasian, 23.3% African-American	All spouses	Mean duration = 69 months, SD = 28.9 Mean level: 11.6 hours/day, SD = 6.9	Salivary cortisol (4 times beginning 2h after arising and ending 2h before their reported time of retiring for the night)	CG events: ↑ Cortisol production
De Vugt et al. (2005)	-CG: N = 57 -Non-CG: N = 55	-CG: Mean age = 60.4, range = 34-81 F = 36, M = 21 -Non-CG: Mean age = 60.5, range = 31-85 F = 36, M = 19 -	28 spouses, 26 children, 3 other	Mean duration = 31.1 months (range = 3-120 months) Mean level = 85.6 hours per week (range = 2-168)		CG: ↑ cortisol at awakening, with smaller ↑ after awakening. Higher cortisol awakening response in CG of patients with ↑ behavioral and psychological symptoms of dementia (BPSD)

Epel et al. (2010)	-CG: N = 22 -Non-CG: N = 22	Mean age = 62, range = 51-75 All female 84% Caucasian, 5% African American, and 11% Asian	All spouses/ partners	Level: at least 4 hours/day	Salivary cortisol (in response to stressor)	CG had similar baseline cort levels and peak cortisol reactivity, but earlier onset of cortisol reactivity
Fonareva et al. (2011)	-CG: N = 20 -Non-CG: N = 20	-CG: Mean age = 64.5, SD = 7.13 F = 18, M = 2 -Non-CG: Mean age = 66.95, SD = 7.89 F = 18, M = 2 97.5% White	70% spouses, 30% children	-	Salivary cortisol (bedtime, waking, 30 minutes post waking),	CG: ↑ salivary cortisol at waking only
Gallagher-Thompson	-CG: N =83 -Non-CG: N = 39 Subsample of	-CG: Age range: 40-70 years 20 Hispanic and 24 non-Hispanic white	-	-	Salivary cortisol three saliva samples daily for	CG: ↑ 8 AM, 5 PM, and 9 PM cortisol. Both ethnicity and depressive symptoms

et al. (2006)	17 Hispanic and 28 non-Hispanic white participants matched on age and education used for main analyses.	-Non-CG: 19 Hispanic and 20 non-Hispanic white All female			3 consecutive days.	independently predicted daytime cortisol slope.
Holland et al. (2010)	-CG: N = 47	Mean age = 59.5, SD = 12.8 Female Chinese	54.5% Daughter, 38.6% spouse, 6.8% daughter-in-law	Duration = About 4 years Mean level = 9.8 hours/day, SD = 7.9	Salivary cortisol (wake, 5pm, 9pm)	Belief in Asian values predicted cort: ↑ cortisol at wake: steeper descent (i.e. less dysregulated)
Irwin et al. (1997)	-CG: N = 100 -Non CG: N = 33	-CG: Mean age = 71, SD = 7.2 F= 57%, M= 43%	All spouses	Mean duration = 2.1 years, SD = 1.2	Plasma ACTH, cortisol	CG: no difference in ACTH, cortisol. Dementia severity did not

		87% White, 4% Black, 5% Hispanic, 4% Asian -Non-CG: Mean age = 69.6, SD = 6.2 F = 58%, M = 42% 100% White				predict cortisol. Demand/respite mismatch predicted ACTH only
Jeckel et al. (2010)	-CG: N = 41 -Non-CG: N = 33	-CG: Mean age = 60.56, SD = 16.56. F = 32, M = 9 -Non-CG: M = 60.27, SD = 14.1 F = 26, M = 7 -	All spouses	Mean duration = 4.03 years, SD = 2.89 Mean level = 16 hours/day, SD = 5.73	Salivary cortisol & DHEA-S (8.00, 12.00, 20.00), HPA response to dexamethasone suppression test (DST)	CG: ↓ cortisol at 8.00, ↓ DHEAS & ↑ cort/DHEAS. More cortisol non-suppressors among CG in response to DST.
Klein et al. (2014)	-CG: N = 158	Mean age = 61.59, SD = 10.54 F = 87.3% 74.1% White	58.2% children, 38% spouses	Mean duration = 62.05 months, SD = 46	Salivary cortisol (wake, wake + 30 minutes, before	CG with negative CAR on non-ADS days had positive CAR on ADS days, CG with flat CAR or

					lunch, before dinner, before bed)	medium-high CAR on non-ADS days had increased CAR on ADS days, and CG with high CAR on non-ADs days had reduced CAR on ADS days (similar pattern for AUCg data)
Leggett et al. (2014)	-CG: N = 164	-CG: Mean age = 61.79, SD = 10.47 F = 87.2% 72.6% White, 25,6% African American, 1.8% Other	38.4% spouses, 57.3% children, 4.2% other	Mean duration = 61.56 months, SD = 46.2	CAR Cortisol area under the curve with respect to ground (AUCg)	↑ anger scores on days when AUCg below average Model 2: anger associated with ↑ care-related stressors, not with ADS use or daily cortisol. Depressed mood associated with more care-related stressors and a low average CAR.

Malarkey et al. (1996)	-CG: N = 10 -Non-CG = 16 (10 completed acute stressor, 6 did not)	Mean age = 69 All female -	All spouses	-	Plasma cortisol, ACTH	CG: ↑ ACTH. CG: no difference in cort. CG did not differ in stress response on these variables
McCallum et al. (2006)	-CG: N = 54 -Non-CG: N = 63	-CG: African-American: Mean age = 58.17, SD = 8.3, European American: Mean age = 67.5, SD = 10.95 30 African American and 24 European American -Non-CG: African-American: Mean age = 59. European American: Mean age = 71 48 AA, 15 European American All female	AA: 66% children, 16% spouses, European: 25% children, 75% spouses	Level: At least 10 hours/week	Salivary diurnal cortisol Participants also collected five saliva samples daily for two consecutive days	Only age and ethnicity predicted cortisol slope

Merritt & McCallum (2011)	-CG: N = 54 -Non-CG: N = 63	-CG: African-American: Mean age = 58.2, SD = 8.3, White: Mean age = 67.2, SD = 10.2 -Non-CG: AA: Mean age = 59 White Mean age = 71 All female -CG: 30 African-American, 24 White, -Non-CG: 48 African-American, 15 White	-AA: 67% children, -White: 26% children	-AA: Mean duration = 60.13 months, SD = 54.38, -White: Mean duration = 70.39, SD = 31.2 Level: at least 10 hours/week	Saliva cortisol (wake, 9am, 12noon, 5pm 9pm)	John Henryism coping associated with flatter cortisol slope. For high JHAC AA, CG status predicted flatter cortisol slope.
Merritt & McCallum (2013)	-CG: N = 30 -Non-CG: N = 48	-CG Mean age: 58.2, SD = 8.3 -Non-CG: Mean age = 59.6, SD = 10.7 All female All African-American	67% children	Mean duration = 60.1 months, SD = 54.4 Level: at least 10 hours per week	Saliva cortisol (wake, 9am, 12noon, 5pm 9pm)	↑ religious coping = flatter cortisol slope (specifically at higher memory/behaviour problems)

Mills et al. (1997)	-High stress CG: N = 10 -Low-stress CG: N = 17 -Non CG: N = 10	-High stress CG: Mean age = 72, SD = 5 F = 8, M = 2 -Low stress CG: Mean age = 75, SD = 7 F = 13, M = 4 -Non-CG: Mean age = 74, SD = 7 F = 2, M = 8 -	All spouses	-	Plasma cort	CG with high life stress: no change in plasma cort.
Neri et al. (2007)	-CG (BPSD): N = 10 -CG (hip fracture/HF): N = 10	CG (BPSD): M = 60.6, SD = 7.9 F = 8, M = 2 CG (HF): M = 49, SD = 8.7 F = 10 CG (res): M = 56.9, SD = 4.6 F = 8, M = 1	-	CG (BPSD): Mean duration = 36.1 months, SD = 23.5	Salivary cortisol	CG showed a reduction in cortisol (between 1 week from entry and 3-7 days before discharge)

	-CG (respite/res): N = 9	-		Mean level = 10.7 hrs/day, SD = 11.2 CG (HF): Mean duration = 59.4 months, SD = 71.1 Mean level = 3.2 hours/days, SD = 2.1 CG (res): Mean duration = 43.3 SD = 38.4 Mean level = 9.6 hrs/day, SD = 4.6		
Oken et al. (2011)	- CG: N = 31	-CG: Mean age = 64.5, SD = 9.3 F = 25, M = 6	23 spouses	Level: minimum 10 hours/week	Morning salivary cortisol	CG: ↑ waking cortisol

	-Non-CG: N = 25	-Non-CG: Mean age = 66.5, SD = 7.6 F = 22, M = 3			(waking, prior to sleep)	
Palma et al. (2011)	-CG: N = 14 -Non-CG: N = 24	-CG: Age range = 66-74 F = 7, M = 7 -Non-CG: Age range = 61-82 F = 20, M = 4	-	Duration: at least 1 year Level: at least 6 hours/day	Salivary cortisol (8.00, 16.00, 22.00)	CG: ↑ cortisol at 22.00 but not at earlier times
Stalder et al. (2014)	-CG: N = 20 -Non-CG: N = 20	-CG: Mean age = 71.2, SD = 6.1 F = 19, M = 1 -Non-CG: Mean age = 72.2, SD = 6.4 F = 17, M = 3 -	20 spouses, 1 child (1 excluded)	Mean duration = 40.8 months, SD = 30.8	Hair cortisol concentration (HCC)	CG: ↑ HCC CG: trend for positive association of HCC with CG burden and positive association with depressiveness.
Tarrier et al. (2002)	-CG: N = 100	Mean age = 63.1 years, SD = 13.6 F = 57, M = 43 -	53 spouses, 36 children, 11 other	Mean duration = 35.2 months, SD = 28.7	Salivary cortisol (9.00a.m and	Strain and distress associated with morning cortisol

				Mean level = 56.1 hours/week ("face-to-face contact"), SD = 30.5	11.00pm for 3 consecutive days)	
Tomiyama et al. (2012)	-CG: N = 14 -Non-CG = 9	Mean age = 62, SD = 6.46 All female 82% White, 11% Asian, 5% Black, 2% Latina	All partners	-	Salivary cortisol (waking, 30 minutes post-waking, bedtime; urine over 12 hr)	CG: no difference in cortisol
Vedhara et al. (1999)	- CG: N = 50 -Non-CG: N = 67	-CG: Median = 73, interquartile range = 66-77 F = 26, M = 24 -Non-CG: Median = 68, interquartile range = 66-71 F = 36, M = 31	All spouses	Mean duration = 3.5 years, SD = 2.7	Salivary cortisol (between 8.00-10.00/before breakfast, 11.00-13.00/before lunch, 20.00-	CG: ↑ AUC for cortisol at baseline, 3 months and 6 months.

		All Caucasian			22.00/at least two hours after evening meal)	
Wahbeh et al. (2008)	-CG: N = 15 -Non-CG: N = 15	-CG: Mean age = 70, SD = 9 F = 9, M = 6 15 White -Non-CG: Mean age =75, SD = 5 F = 10, M = 5 14 White	-	-	Salivary CAR Salivary diurnal cortisol	CG: ↑ cortisol values. Unlike non-CG, cortisol in CG ↑ between awakening and 30 minutes afterward
Wilcox et al. (2005)	-CG: N = 28	-Caucasian CG: N = 16, Mean age =65.69, SD = 10.5 -African-American CG: N = 12, Mean age = 62, SD = 10.2 All female	-Caucasian CG: 8 spouse, 8 children -AA CG: 3 spouse, 7 children, 2 siblings	-Caucasian CG: Mean duration = 47.56 months, SD = 43.89 Mean level = 73.75 hours/week, SD = 56.65	Salivary cortisol	More AA (58%) than Caucasians (14%) showed cortisol reactivity from rest to 15-minutes post-challenge.

				-AA CG: Mean duration = 60 months, SD = 40.97, Mena level = 96.08 hours/week, SD = 42.54		

Table 2: Summary of studies examining effects of family dementia caregiving on the immune system

Article	Sample size	Participant age, gender & ethnicity	Relation to care recipient	Level of care provided	Biomarkers examined	Findings
Adler et al. (2002)	-CG: N = 67	Mean age = 73, range: 56-82 F = 45, M = 22 88% Caucasian	-	-	Total leukocytes Total lymphocytes	Speech stressor ↑ circulating leukocytes, LFA-1 density, ↓ L-selectin density.
Aschbacher et al. (2007)	-CG: N = 51 -Non-CG: N = 27	Mean age = 77, SD = 6.8 All female 95% Caucasian	All spouses	Mean duration = 7.75 years, SD = 2.49	Platelet activation	↑ platelet activation in CG's taking HRT. No main effect of CG on platelet activity.
Aschbacher et al. (2008)	-CG: N = 39 -Non-CG: N = 31	-CG: Mean age = 68.7, SD = 7.99 F = 25, M = 14 -Non-CG: Mean age = 71.87, SD = 7.07	All spouses	Mean duration = 9 years	Percent platelet P-selectin (PSEL)	CG: ↑ symptoms of depression and anxiety associated with ↑ PSEL reactivity, and delayed PSEL recovery. CG: Delayed NE

		F = 22, M = 9 65 Caucasian				recovery associated with ↑ PSEL reactivity and delayed PSEL recovery
Aschbacher et al. (2009)	-CG: N = 99	Mean age = 73 (range = 52-88) F = 68%, M = 32% 93% Caucasian	All spouses	-	PSEL	↑ depression significantly predicted ↑ PSEL activation by stressor
Aschbacher et al. (2013)	-CG: N = 25 -Non-CG: N = 23	Mean age: 63, range = 51-79 All female 43 Caucasian, 4 Asian/Pacific Islander, 1 African-American	-	Mean duration = 4.7 years, range = 8 months - 11.42 years	8-oxoG, 8-OHdG, IsoP	CG: Perceived stress not associated with any oxidative stress markers. Non-CG: perceived stress: ↓ IsoP and trend to ↓ 8-oxoG and 8-OHdG.
Bauer et al. (2000)	-CG: N = 49	Mean age = 72, SD = 7.7 F = 24, M = 25 All Caucasian	All spouses	-	Full blood count Lymphocytes	Elderly CG: ↓ mitogen-induced lymphocyte proliferation, ↓ mitogen-induced IL-2 production,

					Glucocorticoid concentration IL-2	and ↓ lymphocyte sensitivity to glucocorticoids
Bristow et al. (2008)	-CG: N = 25 -Non-CG: N = 36	-CG: Mean age = 62.9, SD = 5.9 F = 76%, M = 24% -Non-CG: Mean age = 63.3, SD = 5.4 F = 69%, M = 31% -	All spouses/ partners	-	Salivary immunoglobulin A (IgA)	CG: no difference in IgA secretion
Cacioppo et al. (1998)	- CG: N = 27 -Non-CG: N = 37	Mean age = 67.17, SEM = 1.03 All female 83% White, 17% Black	All spouses	Level: at least 5 hours/ week	Blood percentages of T lymphocytes (CD3+), two subsets of T lymphocytes (CD4+ and CD8+), and NK	CG: ↓ proliferative response to concanavalin A and a non-significant ↓ in response to PHA. CG: ↓ percentage of NK cell cytotoxicity. No interaction between CG status and acute stressor

					cells (CD56+), NK cell cytotoxicity., mitogen-stimulated PBl activity	
Castle et al. (1995)	-CG: N = 11	-CG: Mean age = 70, SD = 5.7 All female -	All spouses	-	Lymphocytes	Depression strongest association with impaired T cell proliferative capacity. Depression was also most strongly associated with ↑ $CD8^+$ T cells, and a reduced percentage of $CD38^+$ cells in both $CD8^+$ and $CD4^+$ T cell populations. ↓ percentage of CD 38^+ cells correlated with impaired T cell function (proliferation). ↓ in

						natural killer (NK) cells and percentage of $CD56^+$ component of the $CD8^+$ population.
Damjanovic et al. (2007)	-CG: N = 41 -Non-CG: N = 41	Mean age = 65, SD = 1 -CG: F = 30, M = 11 -Non-CG: F = 30, M = 11 -	26 spouses, 15 children	Mean duration = 5.2 years, SD = 0.5	PBMC, T-cells & monocytes: cytokines (IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, IFN-gamma, TNF-alpha)	CG had lower T cell proliferation but higher production of immune-regulatory cytokines (TNF-α and IL-10). Percentage of T/B cells, monocytes and NK cells not sig. different for CG.
Esterling et al. (1994)	-CG: N = 14 -Bereaved CG: N = 17 -Non-CG: N = 31	-CG: Mean age = 68, SEM = 3.21 F = 9, M = 5 -Bereaved CG: Mean age = 72.3 years, SEM = 2.06 F = 12, M = 5	Family	-CG: Mean duration = 62.53 months, SEM = 16 Mean level = 5.08 hour/day	Peripheral blood leukocytes treated with rIL-2 and rIFN-gamma, NK cell and lymphokine-	Continuing and bereaved CG did not differ in NK response to rIL-2 or rIFN-gamma; both worse NK response than non-CG.

		-Non-CG: Mean age = 70.9 years, SEM = 1.82 F = 22, M = 9 94% White		-Bereaved CG: Mean = 26.57 months, SEM = 3.09, since death of care recipient Mean level = 6.97 hour/day.	activated killer cells	
Esterling et al. (1996)	-CG: N = 11 -Bereaved CG: N = 17 -Non-CG: N = 29	- CG: Mean age = 71.5, SEM = 2.97 F = 17, M = 4 -Bereaved CG: Mean age = 61.9, SEM = 3.2 F = 11, M = 6 -Non-CG: Mean age = 68.9, SEM = 1.51	Family members	-CG: Mean duration = 9.6 years. Mean level = 4.2 hours/day. -Bereaved CG: Mean = 36.6 months, SD = 4.46	Enriched NK response to rIL-2 or rIFN-gamma;	CG (both groups): worse NK response in vitro to recombinant IL-2 or IFN-gamma, and worse response to cytokines.

		F = 22, M = 7 90% Caucasian		months since death of care recipient		
Fonareva et al. (2011)	-CG: N = 20 -Non-CG: N = 20	-CG: Mean age = 64.5, SD = 7.13 F = 18, M = 2 -Non-CG: Mean age = 66.95, SD = 7.89 F = 18, M = 2 97.5% White	70% spouses, 30% children	-	CRP, IL-6, TNF-alpha	CG: ↑ CRP, no difference in IL-6 or TNF-alpha
Glaser et al. (1998)	<u>Vaccination 1</u>: -CG = 23 -Bereaved CG = 26 -Non-CG = 27	-CG: Mean age = 71.92, SEM = 1.72 -Bereaved CG: Mean age = 72.65, SEM = 1.7 -Non-CG: Mean age = 70.67, SEM = 1.83	All spouses	Bereaved CG: Mean = 23.84 months, SEM = 3.3 since death of spouse	Antibody titres to influenza vaccine and PBL ability to synthesize IL-2	CG (both groups): ↓ antibody titres to vaccine and more rapid ↓ in PBL ability to synthesize IL-2 after stimulation with Fluzone

		- -				
Glaser et al. (1998)	<u>Vaccination 2:</u> -CG = 32 -Bereaved CG = 22 -Non-CG = 68	-CG: Mean age = 73.12, SEM = 1.53 -Bereaved CG: Mean age = 72.77, SEM = 1.82 -Non-CG: Mean age = 71.54, SEM = 1.05 - -	All spouses	Bereaved CG: Mean = 29 months, SEM = 3.81 since death of spouse	Antibody titres to influenza vaccine and PBL ability to synthesize IL-2	Fewer four-fold responders in CG's
Glaser et al. (1997)	-CG: N = 71 -Non-CG: N = 58	-CG: Mean age = 60.55, SEM = 1.52 F = 58, M = 13 -Non-CG: Mean age = 62.41, SEM = 1.98 F = 45, M = 13	34 spouses, 37 children	Mean duration = 7.66 years, SEM = 4.56 Mean level = 4.86 hours/day, SEM = 5.04	Antibody titres to HSV-1, HSV-1 virus neutralising antibody titres, HSV-1 specific T-	CG: ↑ antibody titres, no difference in neutralising antibody, ↓ proliferative response to HSV-1

		92% White			cell proliferation response	
Glaser et al. (2000)	-CG: N = 11 -Bereaved CG: N = 13 -Non-CG: N = 28	-CG: Mean age = 68.09, SD = 3.8 -Bereaved CG: Mean age = 72.46, SD = 2.29 -Non-CG: Mean age = 69.54, SD = 1.69 F = 39, M = 13 84% White	All spouses	Mean duration: CG: Mean = 6.93 years, SEM = 0.94, Mean level = 8.39 hours/day, SD = 1.98 Bereaved: Mean = 2.08, SEM = 0.5 years since their spouse died	IgC titres in response to vaccination	CG: antibody titres ↓ over 6 months, bereaved CG and non-CG remained the same
Glaser et al. (2001)	-CG: N = 16 -Bereaved CG: N = 16	-CG: Mean age = 71.69, SD = 7.25	All spouses	Duration: CG: Mean = 104.11 months, SEM =	Cytoplasmic cytokines: cells synthesising IL-2,	CG: ↑ percentage of IL-10 in PBL. No difference for cells expressing IL-2 or IFN-gamma.

	-Non-CG: N = 44	-Bereaved CG: Mean age = 77, SD = 9.51 -Non-CG: Mean age = 69.89, SD = 9.26. 71% female 82% Caucasian, 18% African-American		12.31, Mean level = 7.6 hours/day Bereaved: Mean = 2.57 years, SEM = 0.5, since death of spouse	IL-10+ T cells, intercellular IFN-gamma. Percent and number of IL-10/CD-4, IL-10/CD-8, IFN-/CD-4, IFN-/CD-8 and IL-2/CD-4, and IL-2/CD-8 cells	
Gouin et al. (2012)	-CG: N = 53 -Non-CG: N = 77	-CG: Mean age = 64.3, SD = 11.17 F = 79.25%, M = 21.75%. 79.25% Caucasian -Non-CG: Mean age = 65.97, SD = 14.35,	35 children, 18 spouses	Mean duration = 56 months, SD = 44 Mean level = 8.21 hours/day, SD = 7.92	Serum IL-6, CRP	CG: ↑ CRP, no difference on IL-6 levels. Direct effect of CG status on CRP and mediating effect of daily stressors.

		F = 84.41% M = 15.59% 84.41% Caucasian				
Graham et al. (2006)	-CG (continuing & bereaved): N = 113 -Non-CG: N = 101	-CG: Mean age = 69.8, SD = 9.5 F = 69%, M = 31% 90.3% Caucasian -Non-CG: M = 68.2, SD = 9.5 F = 74%, M = 26% 84.2% Caucasian	All spouses	Level: At least 5 hours/week at inclusion	Plasma IL-6 and CRP	In structural equation models, path between bodily pain and CRP was significant for CG but not non-CG.
Irwin et al. (1991)	-CG: N = 48 -Non-CG: N = 17	-CG: Mean age = 71.3, SD = 6.8 F = 30, M = 18 -Non-CG: Mean age = 71.3, SD = 7.3 F = 11, M = 6 -	All spouses	-	NK activity, cytotoxic activity	CG: No effect on NK cell activity, or cytotoxic activity.

Irwin et al. (1997)	-CG: N = 100 -Non CG: N = 33	-CG: Mean age = 71, SD = 7.2 F= 57%, M= 43% 87% White, 4% Black, 5% Hispanic, 4% Asian -Non-CG: Mean age = 69.6, SD = 6.2 F = 58%, M = 42% 100% White	All spouses	Mean duration = 2.1 years, SD = 1.2	NK cell activity	Age (over v. under 70) X CG interaction: non-CG who were younger had lowest NK activity, and younger CG the same as older non-CG.
Jeckel et al. (2010)	-CG: N = 41 -Non-CG: N = 33	-CG: Mean age = 60.56, SD = 16.56. F = 32, M = 9 - -Non-CG: M = 60.27, SD = 14.1 F = 26, M = 7 -	All spouses	Mean duration = 4.03 years, SD = 2.89 Mean level = 16 hours/day, SD = 5.73	PBMC lymphocyte proliferation and steroid sensitivity	CG: ↑ T-cell proliferation, ↑ cellular sensitivity to DEX & corticosterone

Kiecolt-Glaser et al. (1991)	-CG: N = 69 -Non-CG: N = 69	-CG: Mean age = 67.26, SEM = 0.98 F = 49, M = 20 95% Caucasian -Non-CG: M = 67.75, SEM = 0.93 F = 49, M = 20 93% Caucasian	All spouses	Mean duration = 5.2 years, SEM = 0.55 Mean level = 8.26 hours/day, SEM = 0.6	Blastogenesis with two mitogens, concanavalin A (Con A) and phytohemagglutin in (PHA), as well as antibody titres to latent Epstein-Barr virus (EBV), antibodies to EBV virus capsid antigen (VCA) IgG	CG: greater ↑ in EBV, VCA, IgG antibody titres. CG: ↓ blastogenesis in response to ConA and PHA

Kiecolt-Glaser et al. (1995)	-CG: N = 13 -Non-CG: N = 13	-CG: Mean age = 62.3, SEM = 2.3 -Non-CG: Mean age = 60.4, SEM = 2.8 All female -	9 spouses, 4 children	Mean duration = 7.8 years, SD = 0.6 Mean level = 6.7 hours/day, SD = 1.9	Wound healing, IL-1beta mRNA production	Complete wound healing took longer in CG. CG: ↓ IL-1beta mRNA in response to stimulation, specifically LPS (not TNF or GM-CSF)
Kiecolt-Glaser et al. (1996)	-CG: N = 32 -Non-CG: N = 32	-CG: M = 73.12, SD = 8.64 F = 18, M = 14 -Non-CG: M = 73.3, SD = 7.94 F = 18, M = 14 93% Caucasian	All spouses	Mean duration = 7.25 years, SD = 3.46 Mean level = 8.39 hours/day, SD = 8.49	Antibody response (4-fold increase) to vaccination, IL-1beta & IL-6 mononuclear responses to LPS stimulation. % of T-lymphocytes and monocytes	> 70 years old: CG less likely to have antibody response to vaccination, despite comparable baseline antibodies. CG: lower IL-1beta, change following vaccination not sig, no group X time interaction. No effects for IL-6. CG: lower IL-2 (no change in time or group X time). CG: no difference in percentages of

						monocytes, CD3+, CD4+, or CD8+ lymphocytes
Kiecolt-Glaser et al. (2003)	-CG: N = 119 -Non-CG: N = 106	Mean age = 70.58, SD = 8.03. F = 160, M = 65 -	All spouses	Mean duration = 4.91 years, SD = 3.63 Mean level = 9.72 hours/day, SD = 7.7 -Bereaved CG: Mean = 33.71 months, SD = 19 since death of spouse	Plasma IL-6	For both continuing and bereaved CG, IL-6 rise ↑ across the 6 years

Kiecolt-Glaser et al. (2011)	-CG: N = 58 -Non-CG: N = 74	-CG: Mean age = 70.1, SD = 9.41 F = 41, M = 17 -Non-CG: Mean age = 69.34, SD = 10.73 F = 54, M = 20 122 White, 10 Non-White	Spouses and children	-	IL-6 TNF-α	Multiple childhood adversities: ↑ IL-6 Abuse: ↑ IL-6 and TNF-α levels; for TNF-α, this relationship was magnified in CG
Mausbach et al. (2007b)	-CG: N = 106	Mean age = 73, SD = 8.73	All spouses	-	Beta-adrenergic receptor sensitivity	Role overload ↓ beta adrenergic sensitivity, and mastery but not depression mediated this
Mausbach et al. (2007c)	-CG: N = 112 -Non-CG: N = 53	-CG: Mean age = 72.8, SD = 8.7 F= 68%, M = 32% 92% White -Non-CG: Mean age = 67.4, SD = 6.9 F = 76%, M = 24%	All spouses	Mean duration = 3.5 years, SD = 1.1	Plasma t-PA antigen	CG: ↑ t-Pa over time compared with non-CG

		92% White				
Mausbach et al. (2008)	-CG: N = 115	Mean age = 72.6, SD = 8.8 68.7% female 92.2% Caucasian	All spouses	Mean duration = 6 years, SD = 3.5 Mean level: 43.5% less than 7 hrs/day, 33% 7-12hrs/day, 12.2% 13-18 hrs/day, 11.3% 19+ hrs/day	Beta-adrenergic receptors	CG stress negatively associated and CG mastery positively associated with beta-adrenergic sensitivity
Mills et al. (1997)	-High stress CG: N = 10 -Low-stress CG N = 17 -Non CG: N = 10	-High stress CG: Mean age = 72, SD = 5 F = 8, M = 2 -Low stress CG: Mean age =75, SD = 7 F = 13, M = 4	All spouses	-	Beta adrenergic sensitivity	For beta-receptor sensitivity, 30% of the variance was accounted for by high life stress rating, increased age, being male, and lower NE; 17% of the variance in

		-Non-CG: Mean age = 74, SD = 7 F = 2, M = 8				beta-receptor density was accounted for by plasma NE.
Mills et al. (1999)	-Vulnerable CG: N = 10 -Non-vulnerable: N = 10	-Vulnerable CG: Mean age = 74.6, SD = 5 F = 6, M = 4 -Non-vulnerable CG: Mean age = 72.4, SD = 8 F = 6, M = 4 -	All spouses	Level: at least 10 (vulnerable CG) providing more than 12 hrs/day	Lymphocytes Catecholamines	Vulnerable CG: had 60% ↓ L-selectin negative CD8+ T cells (CD8+CD62L-) but no difference in CD8+CD62L+ cells. Vulnerable CG: ↓ CD4+CD62L- T lymphocytes but no difference in CD4+CD62L+ lymphocytes. Acute stressor: ↑ circulating levels of CD8+CD62L- and CD8+CD62L+ lymphocytes and catecholamines similarly in both groups

Mills et al. (2004)	-Vulnerable CG: N = 16 -Non-vulnerable: N = 53 -Non-CG: N = 37	-Vulnerable CG: Mean age = 70.3, SD = 8.6 F = 12, M = 4 -Non-vulnerable: Mean age = 74.8, SD = 8.4 F = 31, M = 22 -Non-CG: Mean age = 68.2, SD = 7.4 F = 30, M = 7 Most White	All spouses	Level: at least 16 (vulnerable CG) providing more than 12 hrs/day	Beta$_2$ receptor sensitivity	Vulnerable CG had lower beta$_2$ receptor sensitivity and density than non-CG (non-vulnerable did not differ from other groups)
Mills et al. (2009)	-CG: N = 81 -Non-CG: N = 41	-Males (N = 34): CG with High CDR: Mean age = 75.6, SD = 9.1 CG with Low CDR: Mean age = 77.8, SD = 3.5	All spouses	-	Plasma IL-6 plasma D-dimer	Males caring for spouse with poorer dementia had ↑ IL-6 levels than non-CG or female CG for worse dementia

		Non-CG: Mean age = 70.5, SD = 8.9 88% Caucasian -Females (N = 88): CG with High CDR: Mean age = 71.3, SD = 9.3 CG with Low CDR: Mean age = 68.5, SD = 8.2 Non-CG: Mean age = 65.7, SD = 6.2 89% Caucasian				
Neri et al. (2007)	-CG (BPSD): N = 10 -CG (hip fracture/HF): N = 10	-CG (BPSD): M = 60.6, SD = 7.9 F = 8, M = 2 -CG (HF): M = 49, SD = 8.7 F = 10 -CG (res): M = 56.9, SD = 4.6	-	CG (BPSD): Mean duration = 36.1 months, SD = 23.5	Salivary IgA, blood IL-2	No overall effect of group on IgA or IL-2

	-CG (respite/res): N = 9	F = 8, M = 1 -		Mean level = 10.7 hrs/day, SD = 11.2 CG (HF): Mean duration = 59.4 months, SD = 71.1 Mean level = 3.2 hours/days, SD = 2.1 CG (res): Mean duration = 43.3 SD = 38.4 Mean level = 9.6 hrs/day, SD = 4.6		

Redwine et al. (2004)	-CG: N = 18 -Non-CG: N = 9	-CG: Mean age = 72.1, F = 89% -Non-CG: Mean age = 67.6 F = 90% -	All spouses	Mean duration = average of 3-5 years	SDF-1, FMLP, ISO	CG: no difference at baseline in chemotaxis to SDF-1, FMLP, ISO, but ↓ SDF-1, FMLP, ISO chemotaxic responses to task
Reese et al. (1994)	-Alzheimer's disease (AD) CG: N = 25 -Stroke (ST) CG: N = 25 -Non-CG: N = 25	-AD CG: M = 56.3, SD = 12.6 F = 19, M = 6 Caucasian = 22, African-American = 3 -ST CG: M = 63.9, SD = 12.9, F = 15, M = 10 Caucasian = 23, African-American = 2 -Non-CG: M = 60.9, SD = 7.4 F = 17, M = 8	-AD CG: 9 spouses, 14 children, 2 other -ST CG: 13 spouses, 10 children, 2 other	-AD CG: Mean duration = 3.7, SD = 1.9 years since diagnosis Mean level = 5.8 hrs/day, SD = 4.3 -ST CG: Mean duration = 3.9, SD = 3.4 years since diagnosis	Immune parameters: CD3+ cells, CD4+ cells, CD8+ cells, NK cells, and total lymphocytes	No group differences in immune data

		Caucasian = 22, African-American = 3		Mean level = 4.4 hrs/day, SD = 2.6		
Scanlan et al. (2001)	-CG: N = 82 -Non-CG: N = 83	-CG: Mean age = 69.8, SD = 7.4 F = 53, M = 29 81 Caucasian, 1 African-American dyad -Non-CG: Mean age =69.1, SD = 5.4 F = 60, M = 23 82 Caucasian, 1 African-American/Asian	All spouses	-Male CG: Mean duration = 45.5 months, SD = 20.8 -Male CG: Mean duration = 52.7 months, SD = 30.6	Lymphocyte response to mitogens	In males, depressed mood factor negatively related to all mitogen responses at T1 and PHA at T2. No relationships occurred in women. At T2 an anger expression factor (anger-out − anger-control) was negatively related to all mitogen responses in CG. Depressed mood at T1 predicted residualised changes in PHA at T2 in men.
Segerstorm et al. (2008)	-CG: N = 14 -Non-CG: N = 30	Mean age = 74.52, SD = 7.11 F = 57% All White	All spouses	Mean duration = 6.57 years, SD = 2.68	Antibody titres. IL-6	CG: no difference in antibody titre to any component of vaccine. CG: ↑ levels of post-vaccination IL-6

Thompson et al. (2004)	-CG: N = 61	-Female: Mean age = 69.7, range = 56-87 -Male: Mean age = 71.4, range = 61-84 F = 45, M = 16 -	All spouses	-Female: Mean duration = 5.8 years, range = 1-12 years -Male: Mean duration = 5.3 years, range = 1-11	Lymphocytes	Male CG had ↑ % NK cells and lower percentage of T helper cells. Female CG had ↓ NK cells than non-CG females (from data bank). In men, ↑ NK cell number correlated with ↓ perceived stress and symptoms.
Vedhara et al. (1999)	- CG: N = 50 -Non-CG: N = 67	-CG: Median = 73, interquartile range = 66-77 F = 26, M = 24 -Non-CG: Median = 68, interquartile range = 66-71 F = 36, M = 31 All Caucasian	All spouses	Mean duration = 3.5 years, SD = 2.7	Influenza IgG antibodies	CG: no difference in antibody concentrations to any vaccine component at baseline. Excluding non-responders, CG had ↓ response to Nanchang strain

Vitaliano et al. (1998a)	- CG: N = 80 -Non-CG: N = 85	-CG: Mean age = 69.8, SD = 8 F = 66%, M = 34% 77 Caucasian, 1 African-American -Non-CG: M = 69.1, SD = 5.6 F = 70%, M = 30% 71 Caucasian, 1 African-American/Asian dyad	All spouses	Mean duration = 43 months, SD = 26	NK cell activity	At time 1, CG with cancer history had lower NK activity (trend at time 2). People with cancer history and high hassles, low uplifts had less NK cell activity.
Vitaliano et al. (2001)	-CG: N = 81 -Non-CG N = 86	-CG: Mean age = 69.8, SD = 7.9 F = 64%, M = 36% 77 Caucasian, 1 African-American -Non-CG: M = 69.1, SD = 5.6 F = 71%, M = 29% 71 Caucasian, 1 African-American/Asian	All spouses		NK activity	CG: no difference in NK activity

Vitaliano et al. (2007)	-CG: N = 130 -Non-CG: N = 125 (at time 1)	-CG: Mean age = 71.7, SD =8.9 F = 62%, M = 38% 94% Caucasian -Non-CG: 70.2, SD = 7.2 F = 64%, M = 36% 92% Caucasian	All spouses	T1: Median duration = 44.1 months, Mean level = 7 hours/day, SD = 8.2	CRP	CG: no difference in CRP.
Von Känel et al. (2006a)	-CG: N = 64 -Non-CG, N = 36	-CG: Mean age = 72.1, SD = 8.7 F = 44, M = 20 -Non-CG: Mean age =68.1, SD = 6.6 F = 26, M = 10 -	All spouses	-	IL-6	CG: ↑ IL-6. After controlling for age and BMI, longer wake time after sleep onset and interaction between caregiver status and higher apnea–hypopnea index were predictors of IL-6.
Von Känel et al. (2006b)	-CG: N = 116 -Non-CG: N = 54	-CG: Mean age = 72.9, SD = 8.7 F = 79, M = 37 -Non-CG: Mean age = 67.6, SD = 6.8	All spouses	-	Plasma IL-6 CRP	CG: ↑ IL-6. CRP levels similar between groups. Age accounted for much of the relationship with IL-6. After controlling for

		F = 40, M = 14 93% Caucasian				covariates, interaction between CG status and age borderline significant for IL-6 (p =.090). CG: age correlated with IL-6.
Von Känel et al. (2010a)	-CG: N = 97 -Non-CG: N = 48	-CG: Mean age = 72.4, SD = 8.7 F = 71%, M = 29% -Non-CG: M = 67.9, SD = 7 F = 73%, M = 27% -	All spouses	-	CRP, IL-6, von Wildebrand factor antigen,	CG: stronger negative correlation between % sleep and IL-6, % sleep and CRP
Von Känel et al. (2012c)	-CG: N = 118 -Non-CG: N = 51	-CG: Mean age = 74.4, SD = 8.1 F = 83, M = 35 -Non-CG: Mean age = 74.4, SD = 5.9 F = 33, M = 18 155 Caucasian	All spouses	Mean duration = 4.4 years, SD = 3.4 Mean level = 7.4 hours/day, SD = 5.8	C-reactive protein (CRP) Tumour necrosis factor (TNF alpha)	↑ duration of caregiving associated with ↑ CRP levels ↑ TNF-α levels in CG ↓ CRP, 3 months after the death of spouse

Von Känel et al. (2014)	-CG: N = 121	Mean age = 74.3, SD = 8 F = 69.4%, M = 30.6%	All spouses	Mean duration = 4.4 years, range = 0.5-17.1	TNF-alpha, IL-8, IFN-gamma, IL-6, CRP	↓ leisure satisfaction and enjoyment from leisure activities: ↑ TNF-alpha, IL-8, IFN-gamma, but not IL-6 or CRP. ↓ frequency of activities: higher IL-8 only
Wu et al. (1999)	-CG: N = 9 -Non-CG: N = 9	CG: Mean age = 64, SD = 1.8 years -Non-CG: Mean age = 68, SD = 2 years All female	All spouses	-	GH mRNA expression in PBMC, B cells compared to T cells	GH mRNA expression in PBMC and B cells ↓ in CG

Table 3: Summary of studies examining effects of family dementia caregiving on cardiovascular measures

Article	Sample size	Participant age, gender & ethnicity	Relation to care recipient	Level of care provided	Biomarkers examined	Findings
Aschbacher et al. (2005)	-CG: N = 60 -Non-CG: N = 33	-CG: Mean age = 72.3, SD = 8.8 F = 63%, M = 37% -Non-CG: Mean age = 68, SD = 7.4 F = 76%, M = 24% 85 Caucasian, 3 Asian, 3 Hispanic, 1 African-American, 1 other	All spouses	-	D-dimer	CG: ↑ D-dimer, but not when depression and anxiety added as covariates
Aschbacher et al. (2006)	-CG: N = 71 -Non-CG: N = 37	-CG: Mean age = 72.58, SD = 8.48 F = 65%, M = 35% 93% White	All spouses	Duration: Six months-10 or more years	D-dimer	Clinical dementia rating: ↑ D-dimer at baseline and in response to stress

		-Non-CG: Mean age = 67.73, SD = 7.11 73% female, 27% male 89% White				
Atienza et al. (2001)	-CG: N = 50	-Female CG: N = 25, Mean age = 70.4, SD = 8.1 92% Caucasian -Male CG: N = 25, Mean age = 72.8, SD = 9.6 92% Caucasian	-Female CG: 22 spouses -Male CG: 22 spouses	Female: Mean = 5 years, SD = 3.4 Mean level = 89.5 hours/week, SD = 48.8 Males: Mean duration = 3.7 years, SD = 3.0 Mean level = 61.5 hours/week, SD = 41.9	HR BP	Female CG: ↑ SBP and DBP reactivity to stress task compared with male CG. No gender differences for ambulatory hemodynamic functioning

Brummet et al. (2013)	-CG: N = 54 -Non-CG: N = 23	Mean age = 62.4, SD = 10.5 F = 79.2%, M = 21.8% 53.3% Caucasian, 46.7% African American	Approximately half were spouses and approximately half were children	A number of years	Metabolic syndrome (Combination of glycosylated hemoglobin concentration (HbA1c%), triglycerides, waist circumference, BP)	Cognitive decline in patient significantly associated with metabolic syndrome in CG
Cacioppo et al. (2000)	-CG: N = 27 -Non-CG: N = 37	Mean age = 67.17, SEM = 1.03 83% White, 17% Black All female	All spouses	Mean level = at least 5 hours/week	BP, HR, cardiac preejection period (PEP), respiratory sinus arrhythmia (RSA)	CG: Higher resting HR, SBP & DBP, and shorter PEPs, but not different in baseline respiration/RSAI. CG showed no

						differences in cardiovascular physiological response
Chattillion et al. (2013)	-CG: N = 66	Mean age = 71.19, SD = 8.71 F = 75.8% 84.85% Caucasian	58 spouses, 2 partners, 6 children	Mean duration: 5.22 years, SD = 4.41 Mean level: 8.15 hours/day, SD = 5.17	Mean arterial pressure, SBP, DBP	CG with ↑ engagement in pleasant events & ↓ perceived activity restriction had ↓ mean arterial BP, SBP & DBP
Clark, et al. (2007)	-New CG: N = 80 -Veteran CG: N = 120 -Non-CG: N = 60	-New CG: Mean age = 73.9, SD = 7.1 62.5% female -Veteran CG: Mean age = 74.2, SD = 7.4 65.8% female -Non-CG: Mean age = 71.9, SD = 7.7	All spouses	-New CG: Mean duration = 5.4 months, SD = 3. -Veteran CG: Mean = 39.7 months, SD = 17.9	Urinary cortisol, EPI NE serum DHEA-S (primary mediators), serum HDL cholesterol	Primary mediators significantly associated with stress- ↑ with time for CG but not non-CG

		68.2% female			total cholesterol blood glycosylated haemoglobin blood pressure, waist-hip ratio (secondary mediators)	
Harmell et al. (2011)	-CG: N = 100	Mean age = 73.8, SD = 8.4	All spouses	Mean duration = 4.23 +/- 3.32 years	Mean arterial pressure, SBP DBP pulse pressure	Coping self-efficacy related to ↓ resting mean arterial pressure, SBP, and pulse pressure, and marginally related to DBP
Irwin et al. (2013)	-CG: N = 32 (10 with hospice	CG (hospice): Mean age = 76.8, SD = 8.68	All spouses	-	BP	Hospice: no difference in SBP or DBP

	prior to death, 22 without)	Non-CG (no hospice): Mean age = 73.95, SD = 8.85 - -				
Jeckel et al. (2010)	-CG: N = 41 -Non-CG: N = 33	-CG: Mean age = 60.56, SD = 16.56 F = 32, M = 9 -Non-CG: M = 60.27, SD = 14.1 F = 26, M = 7 -	All spouses	Mean duration = 4.03 years, SD = 2.89 Mean level = 16 hours/day, SD = 5.73	BP, HR	CG: ↑ DBP & heart rate
Kim et al. (2007)	-CG: N = 160	-White: Mean age = 56.62, SD = 16.35 F = 69.2%, M = 30.8% -African-American: Mean age = 54.71, SD = 15.27 F = 68.4%, M = 31.6%	-	White: Mean duration = 4.63 years, SD = 3.2 Mean level = 19.72 hours/week, SD = 12.99	HR, BP	Buffering effect of active coping on DBP in AA.

		95 African-American, 65 White		AA: Mean duration = 4.07 years, SD = 3.05 Mean level= 16.86 hours/week, SD = 10.57		
King et al. (2002a)	-CG: N = 88	Wives: Mean age = 67.9, SD = 8.7 92.2% white Daughters: Mean age = 56.8, SD = 5.4 85% White All female	52 wives, 36 daughters	Wives: Mean duration = 4.4 years, SD = 3.4, Daughters: Mean duration = 3.5 years, SD = 2.7 Level: At least 10 hours/week	HR BP (ambulatory in response to acute stressor- Submaximal treadmill exercise test + interpersonal interview on CG)	No difference between wives & daughter on acute stressors Daughters had ↑ DBP and HR in presence of care recipient than wives

Knight et al. (2007)	-CG: N = 102 -Non-CG: N = 102	-CG: African-American: Mean age = 57.15, SE = 1.95 White: Mean age = 55.05, SE = 2.67 African-American: F = 45, M = 17 White: F = 25, M = 15 62 AA, 40 White -Non-CG: African-American: Mean age = 57.1, SE = 1.97, White: Mean age = 54.83, SE = 2.7 African-American: F = 45, M = 17, White: F = 25, M = 15 62 AA, 40 White	AA: 23% spouses, 45% children, 31% other White: 30% spouses, 43% children, 25% other	Level: At least 8 hours/week	BP	AA CG: ↑ DBP
Knight and	-CG: N = 154	-White: Mean age = 62.9 years, SD = 12.6	-White: 67 spouse, 33 child, 10 other.	-	Heart rate BP	Race did not modulate SBP reactivity. For DBP, White CG

McCallum (1998)		- African-American: M = 57.7 years, SD = 14.3 -White: F = 78, M = 32 - African-American: F = 36, M = 8 110 White, 44 African-American	-AA: 18 spouse, 20 child, 6 other			showed small ↑, AA males showed ↓, AA females showed larger ↑. Race did not modulate HR
Kring et al. (2010)	-CG: N = 126 -Non-CG: N = 122	-CG: Mean age = 63.2, SD = 13.1 F = 91, M = 35 -Non-CG: Mean age = 60, SD = 14.4 F = 91, M = 31 All White	96% children	-	Serum HDL cholesterol, serum triglyceride levels, waist circumference	For rs439401, CG with TT genotype had worse waist circumference, triglycerides and HDL cholesterol compared to non-CG with TT genotype.
Malarkey et al. (1996)	-CG: N = 10 -Non-CG = 16 (10 completed acute stressor, 6 did not)	Mean age = 69 All female -	All spouses	-	HR, BP, MAP, RSA	CG: ↑ MAP.

Mausbach et al. (2006)	-CG: N = 40	Mean age = 73.3, SD = 8.5 F = 26, M = 14 38 Caucasian	All spouses	-	Plasma D-dimer	↑ wake after sleep onset = ↑ D-dimer
Mausbach et al. (2007a)	-CG: N = 126	Patient mean age = 73, SD = 8.7 F = 68%, M = 32% 92% White, 2.4% Hispanic, 2.4% Asian, 0.8% African-American, 0.8% other	All spouses	-	Plasma D-Dimer	Death/placement in institution led to drop in D-dimer, but only 6 months or more after
Mausbach et al. (2007c)	-CG: N = 112 -Non-CG: N = 53	-CG: Mean age = 72.8, SD = 8.7 F= 68%, M = 32% 92% White -Non-CG: Mean age = 67.4, SD = 6.9 F = 76%, M = 24%	All spouses	Mean duration = 3.5 years, SD = 1.1	MAP	CG: ↑ MAP

		92% White				
Mausbach et al. (2010)	-CG: N = 55 -Non-CG: N = 23	-CG: Mean age = 74.2, SD = 7.6 F = 38, M = 17 White = 50, Hispanic = 4, Black = 1 -Non-CG: Mean age = 74.3, SD = 7.8 F = 18, M = 5 White = 19, Hispanic = 3, Asian = 1	All spouses		Hyperemia induced flow-mediated dilation (FMD)	CG for spouse with moderate to severe dementia: worse FMD than CG for spouse with mild dementia and non-CG ↑ CG duration = ↓ FMD
Mausbach et al. (2012)	-CG: N = 116	Mean age = 74.3, SD = 8.1 F = 68.1%, M = 31.9% 87.1% White, 7.7% Hispanic, 2.6% Black, 0.9% Asian, 1.7% Native American	All spouses	-	Brachial artery flow-mediated dilation (FMD)	More years CG: ↓ FMD

Mills et al. (2009)	-CG: N = 81 -Non-CG: N = 41	-Males (N = 34): CG with High CDR: Mean age = 75.6, SD = 9.1 CG with Low CDR: Mean age = 77.8, SD = 3.5 Non-CG: Mean age = 70.5, SD = 8.9 88% Caucasian -Females (N = 88): CG with High CDR: Mean age = 71.3, SD = 9.3 CG with Low CDR: Mean age = 68.5, SD = 8.2 Non-CG: Mean age = 65.7, SD = 6.2 89% Caucasian	All spouses	-	BP, plasma D-dimer,	Males caring for spouse with poorer dementia had ↑ D-dimer than female CG for worse dementia and compared to non-CG

Redwine et al. (2004)	-CG: N = 18 -Non-CG: N = 9	-CG: Mean age = 72.1, F = 89% -Non-CG: Mean age = 67.6 F = 90% -	All spouses	Mean duration = average of 3-5 years	BP, HR	No difference in baseline BP or HR
Roepke et al. (2011a)	-CG: N = 111 -Non-CG: N = 51	-CG: Mean age = 73.6, SD = 8.2 F = 76, M = 35 102 White, 6 other -Non-CG: Mean age = 74.7, SD = 6.4 F = 35, M = 16 43 White, 7 other	All spouses	Mean duration: 4.2 years, SD = 3.5	BP, carotid artery imaging	CG: ↑ carotid plaques, and poor EPI recovery = ↑ plaque prevalence
Roepke et al. (2011b)	-CG: N = 87 -Non CG: N = 43	-CG: Mean age = 74.3, SD = 7.8 F = 62, M = 25 83 Caucasian, 2 Non-Caucasian	All spouses	Mean duration: 4.3 years, SD = 3.4	Allostatic load (composite of BP, BMI , NE, EPI, cholesterol)	CG: ↑ allostatic load. Mastery, but not depression or overload, moderated the relationship

		-Non-CG: Mean age = 74.9, SD = 6.8 F = 26, M = 17 38 Caucasian, 4 Non-Caucasian				between CG status and allostatic load
Roepke et al. (2012)	-CG: N = 110	Mean age = 73.7, SD = 8.2 F = 76, M = 34 102 Caucasian	All spouses	Mean duration = 4.2 years, SD = 3.5	BP, carotid artery imaging (IMT)	CG duration not a predictor of IMT, but significant predictor of internal/bifurcation IMT
Sakurai et al. (2015)	-CG: N = 20 -Non-CG: N = 20	CG: Median age = 60 (25th-75th percentile: 56-65.8) F = 16, M = 4 Non-CG: Median age = 64.5 (25th-75th percentile: 59.3-69). F = 16, M = 4 -	7 spouses, 10 children, 3 child-in-law	Median duration = 3.9 years (25th-75th percentile = 2.4-5.2)	R-R heart wave	CG: ↑ LF/HF ratio during first half. No difference in HF amplitude. Greater change in HF ratio between first and second half of sleep in CG.

Sarabia-Cobo et al. (2015)	-Family CG: 32 -Pro CG: 42	-Family CG: Mean age = 59.2 F = 86%, M = 14% -Pro CG: Mean age = 42.7 F = 83%, M = 17% -	-	Family CG: Mean duration = 9.8 years Pro CG: Mean duration = 11.7 years	Heart coherence	CG: ↑ burden levels = ↓ heart coherence. Burnout associated with low coherence for professional CG as well. After 3 months' training, no difference found in heart coherence for family v. professional CG. Heart coherence training = ↓ burnout and burden and ↑ heart coherence
Schwartz et al. (2013)	-CG: N = 126	Mean age = 74.16, SD = 7.98 F = 89, M = 37 115 Caucasian, 10 non-Caucasian	All spouses	Mean duration = 4.33 years, SD = 3.38	Dyslipidemia, hypertension	Night time sleep duration, night time sleep efficiency and daytime naps not significantly associated with dyslipidemia, or hypertension

Shaw et al. (1999)	-CG: N = 144 -Non-CG: N = 47	-CG: M = 70.5, SD = 7 F = 93, M = 51 -Non-CG: M = 70.2, SD = 6.4 F = 24, M = 23 -	All spouses	Mean duration = 1.9 years, SD = 1.2 Level: N = 11: no care, N = 44: 1-6 hours/day, N = 24: 7-12 hours/day, N = 31: 13-18 hours/day, N = 29: 19-24 hours/day	BP, HR	CG: no difference in baseline BP, CG: more likely to develop BP readings consistent with borderline hypertension at follow-up. ADL and problem behaviours not significant predictors.
Shaw et al. (2003)	-CG: N = 111	Mean age = 71.6, SD = 6.5 F = 78, M = 33 102 White (non-Hispanic), 3 African American, 3 Hispanic, 3 Asian, Pacific Islander	All spouses	Mean years since AD diagnosis = 4.5 years, SD = 3.3	BP	More problem behaviours and less emotional expression = ↑ DBP. Longitudinal ↑ in DBP predicted by ADL assistance, not emotional

				Mean years since first symptoms = 7, SD = 4.8 Level: N = 9: no care, N = 28: 1-6 hours/day, N = 26: 7-12 hours/day, N = 26: 13-18 hours/day, N = 22: 19-24 hours/day		expression. State hostility unrelated to BP.
Thompson et al. (2004)	-CG: N = 61	-Female: Mean age = 69.7 range = 56-87 -Male: Mean age = 71.4, range = 61-84 F = 45, M = 16 -	All spouses	-Female: Mean duration = 5.8 years, range = 1-12 years -Male: Mean duration = 5.3	Skin conductance HR	Females had ↑ HR, ↓ skin conductance at baseline and during post-stress relax phase

				years, range = 1-11		
Uchino et al. (1992)	-CG: N = 36 -Non-CG: N = 34	Median age = 63.5, range = 30-84 -CG: F = 23, M = 13 -Non-CG: F = 28, M = 6 -	-	Mean duration = 101.97 months Level: At least 5 hours/week	HR BP	CG: comparable age-related increases in SBP and HR. For HR reactivity, social support attenuation age-related ↑, but only in CG
Uchino et al. (1994)	-CG: N = 31	Mean age = 61.87 years F = 18, M = 13 -	20 spouse, 10 children, 1 in-law	Mean duration = 7.35 years Level: At least 5 hours per week	HR BP	Closer affective bonds: ↓ resting DBP. Higher preillness cohesiveness associated with ↑ DBP and SBP
Vitaliano et al. (1998b)	-CG: N = 71 -Non-CG: N = 70	-CG: Mean age = 69.8, SD = 8 F = 66%, M = 34% 70 White, 1 AA	All spouses	Mean duration = 43 months, SD = 27	BP Lipids	CG: ↑ Metabolic syndrome levels, but only those with CHD

		-Non-CG: Mean age = 69.1, SD = 5.6 F = 70%, M = 30% 69 White, 1 African-American /Asian-American dyad				
Vitaliano et al. (2001)	-CG: N = 81 -Non-CG N = 86	-CG: M = 69.8, SD = 7.9 F = 64%, M = 36% 77 Caucasian, 1 African-American -Non-CG: M = 69.1, SD = 5.6 F = 71%, M = 29% 71 Caucasian, 1 African-American/Asian	All spouses		Cardiovascular composite	CG: no difference in cardiovascular composite
Vitaliano et al. (2002)	-CG: N = 72 -Non-CG: N = 80	-CG: Mean age = 71.5, SD = 4.8 F = 48 (20 using HRT, 28 without HRT), M = 24 71 Caucasian, 1 African-American	All spouses	Male: Mean duration = 36.3 months, SD = 21.9	Measures of metabolic syndrome (BP, plasma lipids,	In males, CG had higher obesity and lipids. CG had higher prevalence of CHD

		-Non-CG: Mean age = 69, SD = 5.4 F = 57 (21 using HRT, 36 without HRT), M = 23 79 Caucasian, 1 African-American/Asian dyad		Female w/o HRT: Mean duration = 41.9 months, SD = 24.9 Female using HRT: Mean duration = 55.8, SD = 35.8	insulin, BMI/with obesity)	
Von Känel et al. (2001)	-CG: N = 53	Mean age = 73, range = 59-82 F = 35, M = 18 -	All spouses	-	D-dimer	D-dimer ↑ more in response to acute stress in those with CV disease
Von Känel et al. (2003)	-CG: N = 54	Mean age = 73, SD = 6	All spouses	-	D-dimer	Negative life events associated with greater D-dimer

Von Känel et al. (2005)	-CG: N = 48 -Non-CG: N = 20	-CG: Mean age = 72, SD = 9 F = 30, M = 18 - -Non-CG: Mean age = 68, SD = 7 F = 16, M = 4 -	All spouses	-	D-dimer	CG: higher D-dimer
Von Känel et al. (2006a)	-CG: N = 64 -Non-CG, N = 36	-CG: Mean age = 72.1, SD = 8.7 F = 44, M = 20 -Non-CG: Mean age = 68.1, SD = 6.6 F = 26, M = 10	All spouses	-	D-dimer	CG: ↑ D-dimer. Controlling for age, CG status independently predicted D-dimer levels. Controlling for age and caregiver status, lower sleep efficiency and the interaction between caregiver status and more Stage 2 sleep independently predicted plasma D-dimer levels.

Von Känel et al. (2006b)	-CG: N = 116 -Non-CG: N = 54	-CG: Mean age = 72.9, SD = 8.7 F = 79, M = 37 -Non-CG: Mean age = 67.6, SD = 6.8 F = 40, M = 14	All spouses		D-dimer levels	CG: ↑ D-dimer. Relationship between CG status and D-dimer affected by role overload. After controlling for covariates, interaction between CG status and age significant for D-dimer. CG: age correlated with D-dimer.
Von Känel et al. (2010a)	-CG: N = 97 -Non-CG: N = 48	-CG: Mean age = 72.4, SD = 8.7 F = 71%, M = 29% - -Non-CG: M= 67.9, SD = 7 F = 73%, M = 27% -	All spouses	-	D-dimer	CG: positive correlation between duration of awakenings and D-dimer (not significant when controlling for covariates)
Von Känel et al. (2010b)	-CG: N = 108	Mean age = 74, SD = 8 F = 70%, M = 30% -	All spouses	Duration: N = 33: less than 2 years,	Procoagulent index (sum of standardized z-	↑ problem behaviours and CG negative reaction to behaviours = ↑ procoagulent index

				N = 41: 2-5 years, N = 34: 5 years+	scores of VWF, PAI-1, and D-dimer dividing the sum by 3)	
Wilcox et al. (2005)	-CG: N = 28	-Caucasian CG: N = 16, Mean age =65.69, SD = 10.5 - African-American CG: N = 12, Mean age = 62, SD = 10.2 All female	-Caucasian CG: 8 spouse, 8 children -AA CG: 3 spouse, 7 children, 2 siblings	-Caucasian CG: Mean duration = 47.56 months, SD = 43.89 Mean level = 73.75 hours/week, SD = 56.65 -AA CG: Mean duration = 60 months, SD = 40.97,	BP Heart rate	Race x Task interaction for SBP and HR but not DBP reactivity. AA women showed greater reactivity than Caucasian women.

				Mena level = 96.08 hours/week, SD = 42.54		
Zhang et al. (2006)	-CG: N = 75 -Non-CG: N = 82	-CG: Mean age = 69.8, SD = 8 F = 66%, M = 34% -Non-CG: Mean age = 69.1, SD = 5.6 F = 70%, M = 30% All White	All spouses	-	Risk composite of BP, lipids, BMI, insulin, glucose	CG ↑ risk in males, Cg status did not ↑ risk in females

Table 4: Summary of studies examining effects of family dementia caregiving on epinephrine/norepinephrine

Article	Sample size	Participant age, gender & ethnicity	Relation to care recipient	Level of care provided	Biomarkers examined	Findings
Adler et al. (2002)	-CG: N = 67	Mean age = 73 (Range: 56-82) F = 45, M = 22 88% Caucasian	-	-	EPI NE	Speech stressor ↑ plasma EPI and NE.
Aschbacher et al. (2008)	-CG: N = 39 -Non-CG: N = 31	-CG: Mean age = 68.7, SD = 7.99 F = 25, M = 14 -Non-CG: Mean age = 71.87, SD = 7.07 F = 22, M = 9 65 Caucasian	All spouses	Mean duration = 9 years	Plasma NE	CG: ↑ symptoms of depression and anxiety associated with delayed NE recovery.

Cacioppo et al. (2000)	-CG: N = 27 -Non-CG: N = 37	Mean age = 67.17, SEM = 1.03 83% White, 17% Black All female	All spouses	Mean level = at least 5 hours/week	Plasma EPI NE	CG: Not different in baseline plasma EPI/NE or EPI/NE in response to stress
Chattillion et al. (2012)	- CG: N = 107	Mean age = 73.95, SD = 8.12 years F = 73, M = 34 Caucasian = 101, Other = 5	All spouses	Mean level = 7.6 hours/day, SD = 5.91	EPI NE	CG with ↓ leisure satisfaction: time caregiving positively associated with plasma NE and EPI.
Clark, et al. (2007)	-New CG: N = 80 -Veteran CG: N = 120 -Non-CG: N = 60.	-New CG: Mean age = 73.9, SD = 7.1 62.5% female -Veteran CG: Mean age = 74.2, SD = 7.4 65.8% female -Non-CG: Mean age = 71.9, SD = 7.7	All spouses	-New CG: Mean duration = 5.4 months, SD = 3. -Veteran CG: Mean = 39.7 months, SD = 17.9	Urinary cortisol, EPI NE serum DHEA-S (primary mediators),	Primary mediators significantly associated with stress-↑ with time for CG but not non-CG

		68.2% female				
Ho et al. (2014)	-CG: N = 84	-CG: Mean age = 70.7, SD = 8.46 F = 75%, M = 25% 86.9% Caucasian, 13.1% other	All spouses	Mean duration = 4.9 years, SD = 4.1 years	Resting EPI NE	Mean duration of CG a significant predictor of EPI, not NE. Activity restriction did not predict EPI, with a trend for NE. Years predicted EPI but not NE when CG activity restriction ↑
Irwin et al. (1991)	-CG: N = 48 -Non-CG: N = 17	-CG: Mean age = 71.3, SD = 6.8 F = 30, M = 18 -Non-CG: Mean age = 71.3, SD = 7.3 F = 11, M = 6 -	All spouses	-	EPI NE	CG: No difference in EPI or NE. CG did not differ for dynamic activity of NE/EPI following orthostatic challenge

Irwin et al. (1997)	-CG: N = 100 -Non CG: N = 33	-CG: Mean age = 71, SD = 7.2 F= 57%, M= 43% 87% White, 4% Black, 5% Hispanic, 4% Asian -Non-CG: Mean age = 69.6, SD = 6.2 F = 58%, M = 42% 100% White	All spouses	Mean duration = 2.1 years, SD = 1.2	EPI NE	CG: EPI, NE. Dementia severity did not predict physiological variables.
Malarkey et al. (1996)	-CG: N = 10 -Non-CG = 16 (10 completed acute stressor, 6 did not)	Mean age = 69 All female -	All spouses	-	EPI NE	CG: no difference in EPI/NE. CG did not differ in stress response
Mausbach et al. (2005)	-CG: N = 55	-CG: Mean age = 72.64, SD = 8.46 F = 39, M = 16	All spouses	-	NE	Depressive symptoms predicted post-stressor NE change after controlling for age, CG distress,

		51 Caucasian, 2 Asian, 1 Hispanic, 1 Other				hypertension, and care recipient cognitive function. Depressive symptoms associated with ↑ plasma NE response to psychological stress task
Mausbach et al. (2006)	-CG: N = 40	Mean age = 73.3, SD = 8.5 F = 26, M = 14 38 Caucasian	All spouses	-	EPI NE	↑ wake after sleep onset = ↑ NE No association between sleep variables and EPI
Mills et al. (1997)	-High stress CG: N = 10 -Low-stress CG N = 17 -Non CG: N = 10	-High stress CG: Mean age = 72, SD = 5 F = 8, M = 2 -Low stress CG: Mean age = 75, SD = 7 F = 13, M = 4	All spouses	-	Plasma NE	CG with high life stress: ↑ plasma NE

		-Non-CG: Mean age = 74, SD = 7 F = 2, M = 8 -				
Mills et al. (1999)	-Vulnerable CG: N = 10 -Non-vulnerable: N = 10	-Vulnerable CG: Mean age = 74.6, SD = 5 F = 6, M = 4 -Non-vulnerable CG: Mean age = 72.4, SD = 8 F = 6, M = 4 -	All spouses	Level: at least 10 (vulnerable CG) providing more than 12 hrs/day	EPI	Resting plasma EPI levels ↑ vulnerable CG than non-vulnerable. Acute stressor: ↑ circulating levels of EPI similarly in both groups
Redwine et al. (2004)	-CG: N = 18 -Non-CG: N = 9	-CG: Mean age = 72.1 F = 89% -Non-CG: Mean age = 67.6 F = 90% -	All spouses	Mean duration = average of 3-5 years	EPI NE	CG: no difference in baseline EPI or NE

Roepke et al. (2008)	-CG: N = 68	Mean age = 72.8, SD = 8.8 F = 45, M = 23 63 Caucasian, 5 non-Caucasian	All spouses	-	Plasma NE	ADL: Associated with heightened NE reactivity to speech stressor. Mastery ↓ NE recovery
Roepke et al. (2011a)	-CG: N = 111 -Non-CG: N = 51	-CG: Mean age = 73.6, SD = 8.2 F = 76, M = 35 102 White, 6 other -Non-CG: Mean age = 74.7, SD = 6.4 F = 35, M = 16 43 White, 7 other	All spouses	Mean duration: 4.3 years, SD = 3.5	NE, EPI, carotid artery imaging	CG: Poor EPI recovery = ↑ plaque prevalence
Roepke et al. (2011b)	-CG: N = 87 -Non CG: N = 43	-CG: Mean age = 74.3, SD = 7.8 F = 62, M = 25 83 Caucasian, 2 Non-Caucasian -Non-CG: Mean age = 74.9, SD = 6.8 F = 26, M = 17	All spouses	Mean duration: 4.3 years, SD = 3.4	Allostatic load (composite of BP, BMI , NE, EPI, cholesterol)	CG: ↑ allostatic load. Mastery, but not depression or overload, moderated the relationship between CG status and allostatic load

		38 Caucasian, 4 Non-Caucasian				

Table 5: Summary of studies examining effects of family dementia caregiving on neurocognition and neurotrophins

Article	Sample size	Participant age, gender & ethnicity	Relation to care recipient	Level of care provided	Biomarkers examined	Findings
Burns, et al. (2002)	-CG: N = 33 -Non-CG: N = 33	-CG: Mean age = 55.6, SD = 13.5 F = 82%, M = 18% 73% Caucasian, 27 African-American -Non-CG: Mean age = 55.4, SD = 14.1 F = 82%, M = 18% 73% Caucasian, 27 African-American	First degree relative, spouse or in-law	-	Concentration and problem solving (Proofreading task, Embedded Figure Test)	CG ↓ time on the embedded figures test CG: Trend for missing more errors on proofreading test.
Caswell et al. (2003)	-CG: N = 44 -Non-CG: N = 66	-CG: Mean age = 74.27, SD = 7.91 F = 52.3%, M = 47.7%	All spouses	-	Information processing speed, concentration and	CG: ↓ DST overall performance. Explained by CG status as well as age and education, but no longer

		-Non-CG: Mean age = 70.85, SD = 6.32 F = 68.2%, M = 31.8%. All Caucasian			attention (Digit symbols test; DST)	significant when distress was added to equation
Correa et al. (2015)	-CG: N = 17 -Non-CG: N = 18	-CG: Mean age: 64.83, SEM = 3.64 F = 13, M = 5 -Non-CG: Mean age = 58.29, SEM = 3.16 F = 14, M = 3 -	-	Duration: at least one year Level: at least 8 hours per day	Logical/episodic Memory (Story recall), Working memory (Digit Span), Executive function (Trail Making)	CG: ↓ cognitive performance (Digit Span and Trail Making B post-covariate adjustment)
De Vugt et al. (2006)	-CG: N = 54 -Non-CG: N = 108	-CG: Mean age = 68.4, SD = 8.5 F = 59.3%, M = 40.7% -Non-CG: Mean age = 68.3, SD 8.4 F = 59.3%, M = 40.7%	All spouses	Median duration = 24 months, range = 3-120 months	Verbal memory (Auditory verbal learning test), info processing speed (letter digit coding	CG: ↓ performance in delayed recall and speed of information processing, trend for ↓ performance in cognitive flexibility. CG did not differ in IQ

		-		Mean level = 153.6 hours/week, SD = 14.1	test), Stroop (cognitive flexibility), IQ (Groninger Intelligence Test-short)	
Oken et al. (2011)	- CG: N = 31 -Non-CG: N =25	-CG: Mean age = 64.5, SD = 9.3 F = 25, M = 6 -Non-CG: Mean age = 66.5, SD = 7.6 F = 22, M = 3	23 spouses	Level: minimum 10 hours/week	Attention (Attention network test), cognitive flexibility (Stroop), verbal memory (CERAD word list)	CG: ↓ performance Attention network test and Stroop, no difference in verbal memory

Palma et al. (2011)	-CG: N = 14 -Non CG: N = 24	-CG: Age range = 66-74 F = 7, M = 7 -Non-CG: Age range = 61-82 F = 20, M = 4	-	Duration: at least 1 year Level: at least 6 hours/day	Logical/episodic Memory (Story recall)	CG: ↓ recall, memory ↑ for emotionally valenced story only for non-CG.
Vitaliano et al. (2009)	-CG: N = 130 -Non-CG: N = 13	-CG: Mean age = 71.7, SD = 8.9 F = 62%, M = 38% 94% White -Non-CG: Mean age = 70.2, SD = 7.2 F = 64%, M = 32% 92% White	All spouses	Median duration = 44.1 months Mean level = 7 hours/day, SD = 8.2	Information processing speed, concentration and attention (DST)	CG: ↓ DST scores at T1, 1-tear and 2-year follow-up, and declined 4.5 times faster than non-CG
Vitaliano et al. (2007)	-CG: N = 130 -Non-CG: N = 125 (at time 1)	-CG: Mean age = 71.7, SD = 8.9 F = 62%, M = 38% 94% Caucasian -Non-CG: 70.2, SD = 7.2	All spouses	Mean level = 7 hours/day, SD = 8.2 (At T1)	Information processing speed, concentration and attention (DST)	CG: ↓ DST at T1 and 2-year follow-up

		F = 64%, M = 36% 92% Caucasian				

Table 6: Summary of studies examining effects of family dementia caregiving on other markers of stress

Article	Sample size	Participant age, gender & ethnicity	Relation to care recipient	Level of care provided	Biomarkers examined	Findings
Aschbacher et al. (2007)	-CG: N = 51 -Non-CG: N = 27	Mean age = 77, SD = 6.8 All female 95% Caucasian	All spouses	Mean duration = 7.75 years, SD = 2.49	BMI	CG: No sig difference for BMI
Bauer et al. (2000)	-CG: N = 49	Mean age = 72, SD = 7.7 F = 24, M = 25 All Caucasian	All spouses	-	BMI	CG: No sig difference for BMI
Brummet et al. (2005)	-CG: N = 147 -Non-CG: N = 147	-CG: Mean age = 60.6, SD = 13.1 F = 110, M = 37 38 African-American -Non-CG: Mean age = 55.7, SD = 14.3 F = 111, M = 36	96% children	Duration: Majority active for 3 months or longer	Plasma glucose	CG: ↑ glucose for those with worse neighbourhood characteristics

		42 African-American				
Da Roza Davis et al. (2001)	-CG: N = 30 -Non-CG: N = 28	-CG: Mean age = 68.8, range = 30-75 years F = 18, M = 12 -Non-CG: Mean age = 68.1, range = 35-84 years F = 17, M = 11 -	-	-	Plasma tryptophan	CG: ↓ total tryptophan, no difference in free tryptophan
Damjanovic et al. (2007)	-CG: N = 41 -Non-CG: N = 41	Mean age = 65, SD = 1 -CG: F = 30, M = 11 -Non-CG: F = 30, M = 11 -	26 spouses, 15 children	Mean duration = 5.2 years, SD = 0.5	PBMC telomere length, telomerase activity	CG: ↓ telomere lengths in PBMC. CG: ↑ basal telomerase activity in PBMC and T cells
Epel et al. (2010)	-CG: N = 22 -Non-CG: N = 22	Mean age = 62, range = 51-75 All female 84% Caucasian, 5% African American, and 11% Asian	All spouses/ partners	Level: at least 4 hours/day	PBMC telomerase activity	CG: ↓ telomerase activity at baseline and ↓ telomerase activity across timepoints. Similar ↑ in

						telomerase activity in response to acute stress
Fonareva et al. (2011)	-CG: N = 20 -Non-CG: N = 20	-CG: Mean age = 64.5, SD = 7.13 F = 18, M = 2 -Non-CG: Mean age = 66.95, SD = 7.89 F = 18, M = 2 97.5% White	70% spouses, 30% children	-	Sleep polysomnography	CG: ↑ sleep time in stage N1, ↓ in stage R, similar time in stages N2 and N3
Kiecolt-Glaser et al. (2011)	-CG: N = 58 -Non-CG: N = 74	-CG: Mean age = 70.1, SD = 9.41 F = 41, M = 17 -Non-CG: Mean age = 69.34, SD = 10.73 F = 54, M = 20 122 White, 10 Non-White	Spouses and children	-	Telomere length	Multiple childhood adversities: ↓ telomere length
Kring et al. (2010)	-CG: N = 126	-CG: Mean age = 63.2, SD = 13.1 F = 91, M = 35	96% children	-	Plasma glucose, serum insulin	No significant difference in glucose/insulin

	-Non-CG: N = 122	-Non-CG: Mean age = 60, SD = 14.4 F = 91, M = 31 All White				
Mills et al. (2009)	-CG: N = 81 -Non-CG: N = 41	-Males (N = 34): CG with High CDR: Mean age = 75.6, SD = 9.1 CG with Low CDR: Mean age = 77.8, SD = 3.5 Non-CG: Mean age = 70.5, SD = 8.9 88% Caucasian -Females (N = 88): CG with High CDR: Mean age = 71.3, SD = 9.3	All spouses	-	Sleep polysomnography	Males caring for spouse with more severe dementia had more time awake after sleep onset (WASO) and trend for poorer sleep efficiency than female CG for worse dementia

		CG with Low CDR: Mean age = 68.5, SD = 8.2 Non-CG: Mean age = 65.7, SD = 6.2 89% Caucasian				
Roepke et al. (2011a)	-CG: N = 111 -Non-CG: N = 51	-CG: Mean age = 73.6, SD = 8.2. F = 76, M = 35 102 White, 6 other -Non-CG: Mean age = 74.7, SD = 6.4 F = 35, M = 16 43 White, 7 other	All spouses	Mean duration: 4.2 years, SD = 3.5	Sleep actigraphy	CG: No difference in sleep efficiency
Sakurai et al. (2015)	-CG: N = 20 -Non-CG: N = 20	-CG: Median age = 60 (25th-75th percentile: 56-65.8) F = 16, M = 4	7 spouses, 10 children, 3 child-in-law	Median duration = 3.9 years (25th-75th percentile = 2.4-5.2)	Sleep actigraphy	CG: No difference in sleep latency, time, efficiency, or wake after sleep onset

		-Non-CG: Median age = 64.5 (25th-75th percentile: 59.3-69). F = 16, M = 4 -				
Thompson et al. (2004)	-CG: N = 61	-Female: Mean age = 69.7, range = 56-87 -Male: Mean age = 71.4, range = 61-84 F = 45, M = 16 -	All spouses	-Female: Mean duration = 5.8 years, range = 1-12 years -Male: Mean duration = 5.3 years, range = 1-11	Skin temperature	Women had ↓ skin temp at baseline and during post-stress relax phase
Tomiyama et al. (2012)	-CG: N = 14 -Non-CG = 9	Mean age = 62, SD = 6.46 All female 82% White, 11% Asian, 5% Black, 2% Latina	All partners	-	PBMC telomere length BMI	CG: no difference in telomere length or BMI

Vitaliano et al. (1996a)	-CG: N = 81 -Non-CG: N = 86	-CG: Mean age = 69.8, SD = 8 F = 64%, M = 36%. 80 White, 1 African-American -Non-CG: Mean age = 69.1, SD = 5.6 F = 70%, M = 30% 85 White, 1 African-American/Asian dyad	All spouses	-Male CG: Mean duration = 40.1 months, SD = 24.8 -Female CG: Mean duration = 47.2 months, SD = 29.5	BMI	Male CG: ↑ BMI at T1 and T2. Female CG: No difference in BMI, but gained more weight between T1 and T2
Vitaliano et al. (1996b)	-CG: N = 78 -Non-CG: N = 72	-CG: Mean age = 69.8, SD = 7.4 F = 47, M = 26 77 Caucasian, 1 African-American. -Non-CG: Mean age =69.1, SD = 5.4 F = 50, M = 22.	All spouses	-Male CG: Mean duration = 45.5 months, SD = 20.8 -Female CG: Mean duration = 69.1 months, SD = 5.4	Insulin Glucose	CG: ↑ hostility = ↑ glucose

		71 Caucasian, 1 African-American/Asian				
Vitaliano et al. (1996c)	-CG: N = 78 -Non-CG: N = 72	-CG: Mean age = 69.8, SD = 7.4 F = 65%, M = 35% 77 Caucasian, 1 African-American. -Non-CG: Mean age =69.1, SD = 5.4 F = 69%, M = 31% 71 Caucasian, 1 African-American/Asian dyad	All spouses	-Male CG: Mean duration = 45.5 months, SD = 20.8 -Female CG: Mean duration = 52.7 months, SD = 30.6	Insulin Glucose	Differences in psychological distress mediated higher insulin in CG at T2. CG: no difference in glucose, but psychological distress = ↑ glucose at T2 (controlling for T1)
Vitaliano et al. (2005)	-CG: N =110 -Non-CG: N = 105	-CG: Mean age = 72.2, SD = 9.3 F = 60%, M = 40% 93% Caucasian, 7% non-Caucasian	All spouses	-	Glucose, insulin, BMI	CG: ↑ insulin, glucose, obesity

		-Non-CG: Mean age = 71, SD = 6.9 F = 62%, M = 38% 94% Caucasian, 6% non-Caucasian				
Von Känel et al. (2010a)	-CG: N = 97 -Non-CG: N = 48	-CG: Mean age = 72.4, SD = 8.7 F = 71%, M = 29% -Non-CG: M= 67.9, SD = 7 F = 73%, M = 27% -	All spouses	-	Sleep actigraphy	CG: ↓ % sleep, wake after sleep onset, ↑ duration of awakenings
Von Känel et al. (2012a)	-CG: N = 109 -Non-CG: N = 48	-CG: Mean age = 74.1, SD = 8.1 F = 69.7%, M = 30.3% -Non-CG: Mean age = 74.7, SD = 6 F = 62.5%, M = 37.5% 92% Caucasian, 8% other	All spouses	Mean duration = 4.5 years, SD = 3.5 years	Sleep actigraphy	Spousal death ↑ CG night time wake after sleep onset & daytime total sleep time. Night time sleep percent ↓. Night time total sleep time did not change. Placement of

						spouse had no significant effect on CG sleep.
Von Känel et al. (2012b)	-CG: N = 119 -Non-CG: N = 58	-CG: Mean age = 74.4, SD = 8.1 F = 69.7%, M = 30.3% 113 Caucasian -Non-CG: Mean age = 74.9, SD = 6.2 F = 67.2%, M = 32.8% 50 Caucasian, 5 African American, 9 Other	All spouses	Mean duration = 4.4 years, SD = 3.4	Glomerular filtration rate (GFR)	CG: No difference in change in GFR at follow-up. GFR ↓ disproportionately 3 months after placement of spouse in nursing home. Effect stronger in CG with hypertension or ↑ DBP levels
Zhang et al. (2001)	-CG: N = 93 -Non-CG = 91	-CG: M = 69.9, SD = 7.4 F = 66%, M = 34% -Non-CG: M = 69.1, SD = 5.4 F = 71%, M = 29% All Caucasian	All spouses	Male CG: Mean duration = 45.5 months, SD = 20.8 Female CG: Mean duration = 52.7 months, SD = 30.6	Glucose	Higher Sense of coherence = ↓ glucose in males (both CG and non-CG)

Table 7: Studies examining interventions to reduce impact of dementia caregiving on biomarkers of stress

Article	Intervention	Sample size	Participant age, gender & ethnicity	Relation to care recipient	Level of care provided	Biomarkers examined	Findings
Aboulafia-Brakha et al. (2014)	Cognitive behavioural therapy (CBT) v Psycho-education (PE)	-CBT: N = 12 -PE: N = 15	-CBT: Mean age: 59.42, SD = 6.67 All female - -PE: Mean age = 55.07, SD = 10.68 F = 10, M = 5 -	-CBT: 9 spouses, 2 children, 1 other -PE: 12 spouses, 2 children, 1 other	-CBT: Mean level = 6 hours/day, SD = 2.09 PE: Mean level = 5.40 hours per day, SD = 2.35	Salivary cortisol	CBT: ↓ salivary cortisol levels post-intervention, not in PE
Black et al., (2013)	Kirtan Kriya Meditation (Med) v.	-Med: N = 23 -Music: N = 16	-Med: Mean age = 60.5 SD = 28.2 F = 100%	-	- Med: Mean duration = 4.7 years, SD = 2.4	Genome-wide transcriptional analysis	Med: ↓ expression of genes bearing NF-κB-response elements, and ↑

	relaxing music control (Music)		- -Music: Mean age = 60.6, SD = 12.5 F = 88%, M = 12% -		Mean level= 47.8 hours/week, SD = 35.8 - Music: Mean duration = 4.2 years, SD =2.9 Mean level = 63.3 hours/week, SD = 36.2		expression of genes bearing Interferon Response Factor 1 response elements
Danuclav et al. (2013)	Yoga & Compassion Meditation Program (YCMP).	-YCMP: N = 25 -Control: N = 21	-YCMP: Mean age = 55.5, SD = 8.1 F = 22, M = 3. - -Control: Mean age = 53.4, SD = 8.2	-	-YCMP: Mean duration = 4.2 years, SD = 3.3 –Control: Mean duration = 5.7 years, SD = 3.7	Salivary cortisol (waking, 30 mins post-waking)	YMCP: ↓ cortisol post-intervention, not in control

	v. No treatment control (Control)		F = 19, M = 2. -				
Garand et al. (2002)	Progressively Lowered Stress Threshold (PLST) v. comparison intervention with information, psychological support, community services (comparison)	-CG: N = 37	Mean age = 65.49, SD = 10.75 F = 92%, M = 8% All Caucasian	73% spouses	Mean = 61.51 months ago since diagnosis, SD = 63.17 Mean level: PLST: Mean = 161.57 hours/week, SD = 46.27 Comparison: M = 133.35 hours/ week, SD = 46.27	NK cell cytotoxicity, T-cell proliferation to PHA and concanavalin A	PLST: ↑ T-cell proliferation to PHA and con, including at 6-month follow-up

Grant et al. (2003)	Respite: 10 days of in-home help v. non-respite control	-Vulnerable CG: N = 27 -Non-vulnerable CG: N = 28	-Vulnerable CG: Mean age = 72.07, SD = 6.32 F=55.6%, M=44.4%. 89.3% White, 10.7% non-White -Non-vulnerable CG: Mean age = 74.54, SD = 4.05 F = 67.9%, M = 32.1% 100% White	All spouses	At least 27 providing more than 12 hours/day (vulnerable CG)	BP HR EPI NE	In vulnerable CG, at 1-month follow-up, respite ↓ plasma EPI, but waitlist ↑. No effect for NE, HR, BP
Holland et al. (2011)	Coping with Caregiving (CwC) v.	-CwC: N = 90 -TSC: N = 85	Mean age = 58.21, SD = 13.76 All female	38.3% spouse	Mean duration = 4.24 years, SD = 4.12	Salivary cortisol (waking, 5pm, 9pm)	CG intensity (hours + cohabit): ↓ baseline cort-

	telephone support control (TSC)		53.1 % Caucasian, 46.9% Hispanic /Latino -		Mean level = 10.18 hours/day, SD = 7.2		at waking and flatter across day CwC: no main effect on cort, but high intensity CG had dysregulation reversed by intervention
Innes et al. (2012)	Kirtan Kriya Meditation (Med) (No control condition)	-CG: N = 5 (with 5 care recipients)	Mean age = 71.5, SEM = 5.25 (1 person dropped out) F = 3, M = 3 All non-Hispanic White	5 spouses, 1 daughter	-	BP, heart rate, cognitive status	CG: ↑ retrospective memory and ↓ SBP. Trend for BDP
Kim et al. (2011)	Support program (SP), 8 weeks, 2-	-SP: N = 25 -Control: N = 19	-SP: Age: N = 1: 80+ years, N = 8: 60-69, N = 10: 50-	-SP: 6 Daughters-in-law, 1 son, 10	-SP: Duration of care: 20 = 5 years	EPI, NE	-SP: No sig. change in NE, but was ↑ for control, no effect on EPI.

	3 hours per session v. no intervention (Control)		59, N = 4: 40-49, N = 2: below 40 F = 24, M = 1 - -Control: Age: N = 3: 80+, N = 1: 70-79, N = 10: 60-69, N = 3: 50-59, N = 2: 40-49 F = 16, M = 3 -	daughters, 4 spouses, 4 sisters -Control: 5 daughter-in-laws, 1 son, 3 daughters, 9 spouses, 1 sister	or less, 4 = 6-15, 1 = 16 or more -Control: Duration of care: 9 = 5 years or less, 6 = 6-15, 4 = 16 or more		No baseline difference in EPI/NE.
King et al. (2002b)	Home-based exercise v. nutrition education as attention control	-Exercise: N = 45 -Control: N = 40	-Exercise: Mean age = 62.2, SD = 9.3 -Control: Mean age = 63.3, SD = 9	-Exercise: 55.6% spouse -Control: 50% spouse	Mean duration = 4 years Mean level = 72 hours/week	HR, BP (in response to emotional challenge)	Exercise: ↓ BP reactivity to emotional stressor

			All female 86% White				
Lavretsky et al. (2013)	Kirtan Kriya Meditation (Med) v Music control (Music)	-CG: N = 39 -Med: N = 23 -Music: N = 16	-Med: Mean age = 60.5, SD = 28.2 All female -Control: Mean age = 60.6, SD = 12.5 F = 14, M = 2 -	13 spouses, 36 children (at screening)	-Med: Mean duration = 4.7 years, SD = 2.4 Mean level = 47.8 hours/week, SD = 35.8 -Control: Mean duration = 4.2 years, SD = 2.9 Mean level = 63.3 hours/week, SD = 36.2	Telomerase activity, verbal memory, attention and processing speed, executive function	Med: ↑ MMSE and Trailmaking B (executive function). ↑ telomerase activity

Leach et al. (2015)	Transcendental meditation (TM) course v. waitlist control (waitlist)	-TM: N = 8 -Waitlist: N = 9	-TM: Mean age = 69.4, SD = 7.3. F = 7, M = 1 - -Waitlist: Mean age = 63.2, SD = 8.8 F = 8, M = 1 -	-TM: 5 spouses, 3 children -Waitlist: 6 spouses, 3 children	-TM: Mean duration = 6.75 years, SD = 3.57 Mean level = 118.06 hours/week, SD = 68.9 -Waitlist: Mean duration = 4.21 years, SD = 3.32 Mean level = 125.71 hours/week, SD = 72.27	Cognitive performance (response speed, impulsivity, attention & concentration, information processing efficiency, memory, executive function, emotion identification, emotion bias)	TM: ↑ response speed

McKenzie et al. (2013)	CBT (No control condition)	-CG: N = 12	Mean age = 70.17, SD = 7.15 F = 91.7% All White	All spouses	Mean level = 9.46 hours/day, SD = 9.42	Cognition	CBT: ↑ cognition total index; ↑ attention, immediate and delayed memory
Moore et al. (2013)	Pleasant events program (PEP) v. info support (IS)	-PEP: N = 49 -IS: N = 51	-PEP: Mean age = 70.86, SD = 7.57 F = 81.6%, M = 18.4% 89.8% Caucasian -IS: Mean age = 71.33, SD = 9.08 F = 66.7% M = 33.3% 90.2% Caucasian	Family members	PEP: Mean duration = 5.42 years, SD = 4.91 Mean level = 8.22 hours/day, SD = 5 IS: Mean duration = 3.95 years, SD = 2.41 Mean level = 8.02, SD = 5.38	D-dimer, IL-6	PEP: ↓ IL-6 more than IS, though not maintained at 1-year follow-up No sig difference between treatments for D-dimer.

Oken et al. (2010)	Mindfulness-based cognitive therapy (MBCT), v. educational class adapted from Powerful Tools for Caregivers(PTC) v. respite-only interventions (Control)	-CG: N = 31	-MBCT: Mean age = 62.5, SD = 11.6 F = 8, M = 2 8 White, 1 AA, 1 Asian -PTC: Mean age = 67.1, SD = 8.4 F = 8, M = 3 8 White, 1 Asian -Control: Mean age = 63.8, SD = 7.9 F = 9, M = 1 10 Caucasian	-MBCT: 7 spouses, 3 children -PTC: 8 spouses, 3 children -Control: 8 spouses, 2 children	Level: At least 12 hours/week	Salivary cortisol, cognition (Stroop colour and word test, ANT)	MBCT & PTC: ↑ ANT alerting score. PTC: ↑ Stroop performance No differences in cortisol

Pomykala et al. (2012)	Kundalini Yoga v. relaxation control (RC)	-Yoga: N = 4 -RC: N = 5	-Yoga: Mean age = 56, SD = 10.1. All female - RC: Mean age = 49.8, SD = 3.9 F = 4, M =1 -	-	Yoga: Mean duration = 7.8 years, SD = 2.9 RC: Mean duration = 4.2 years, SD = 3.6 Level: At least 3 days per week	PET	Yoga: ↓ metabolism over time in right inferior frontal cortex, right posterior cingulate cortex, left associative visual cortex. ↑ left superior frontal cortex, right lentiform nucleus, bilateral cerebellar metabolism. Yoga showed smaller ↑ right anterior hippocampus
Vedhara et al. (2003)	Cognitive-behavioural SMI course	-CG: N = 43 -Non-CG: N = 27	-CG: Mean age = 75 years, SD = 7 F = 24, M = 19 42 White/European	All spouses	Mean duration = 4 years, SD = 2 since diagnosis	Saliva cortisol, IgG response to vaccination	CG: no difference on salivary cort. Cortisol highest mid-course. CBT: ↑ IgG response

	(No control condition)		-Non-CG: Mean age = 71 years, SD = 4 F = 14, M = 13 26 White/European		Mean level = 16 hours/day, SD = 6		and more likely to show clinically appropriate level of response to viral strain
Wilkins et al. (1999)	Psycho-education (PE; coping skills + CBT) (No control condition)	-CG: N = 11	Mean age = 70, SD = 5.7 All female 6 Caucasian, 4 AA, 1 Hispanic	All spouses	-	T cell proliferation capacity in response to phytohemaglutinin antigen (PHA)	PE: ↓ immune function post-intervention, but trend for improvement at 1 month follow-up
Williams et al. (2010)	Video-based coping skills (VSC) v. waitlist control (control)	-VSC: N = 59 -Control: N = 57	-VSC: Mean age = 62.1, SD = 13.6 F = 44, M = 15 37 Caucasian, 20 AA, 1 other	-VSC: 30 spouses, 22 children, 7 other	-VCS: Mean = 42 months since diagnosis, SD = 35 -Waitlist: Mean = 45, SD = 32	BP, HR, salivary cortisol (in response to stress and at waking-i.e.	VCS: ↓ DBP and SBP, no effect for BP/HR reactivity to stress. No effect on cortisol

			-Waitlist: Mean age = 59, SD = 12.8 F = 46, M = 11 36 Caucasian, 20 AA	-Control: 17 spouses, 36 children, 4 other		waking, wake +30 mins, after 6pm)	

Table 8: Quality assessment of literature reviewed

Study	Selection bias	Exposure bias	Outcome bias	Confounding bias	Analytical bias	Attrition bias	Overall risk of bias
Aboulafia-Brakha et al. (2014)	Low	High	Minimal	Low	Low	Low	Low-Moderate
Adler et al. (2002)	Moderate	High	Minimal	High	Low	N/A	Low-Moderate
Aschbacher et al. (2005)	Low	High	Moderate	Minimal	Low	N/A	Low-Moderate
Aschbacher et al. (2006)	Moderate	Low	Minimal	Minimal	Moderate	Unclear (moderate)	Low-Moderate
Aschbacher et al. (2008)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Aschbacher et al. (2009)	Moderate	High	Minimal	Minimal	Moderate	Moderate	Moderate
Aschbacher et al. (2013)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Atienza, et al. (2001)	Minimal	Minimal	Minimal	Minimal	Low	N/A	Minimal
Bauer, et al. (2000)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Black et al. (2013)	Low	Low	Minimal	Minimal	Moderate	Low	Low

Bristow, et al. (2008)	Low	High	Minimal	Minimal	High	N/A	Low-Moderate
Brummet et al. (2005)	Minimal	Low	Moderate	Minimal	Low	N/A	Low
Brummet et al. (2007)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Brummet et al. (2008)	Low	High	Minimal	Minimal	Low	N/A	Low-Moderate
Brummet et al. (2013)	Low	High	Moderate	Minimal	Low	Moderate	Moderate
Burns et al. (2002)	Minimal	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Cacioppo et al. (1998)	Minimal	Low	Minimal	Minimal	Moderate	N/A	Low
Cacioppo et al. (2000)	Minimal	Low	Minimal	Minimal	Moderate	N/A	Low
Castle et al. (1995)	Moderate	High	Minimal	High	Moderate	N/A	Moderate
Caswell et al. (2003)	Minimal	High	Minimal	Low	Moderate	N/A	Low-Moderate
Chattillion et al. (2012)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Chattillion et al. (2013)	Low	Low	Minimal	Minimal	Low	N/A	Low
Clark et al. (2007)	Moderate	Low	Moderate	High	Low	Moderate	Moderate
Correa et al. (2015)	Low	Low	Minimal	Minimal	Low	N/A	Low

Da Roza Davis & Cowen (2001)	Minimal	High	Minimal	Low	Moderate	N/A	Low-Moderate
Damjanovic et al. (2007)	Moderate	Low	Minimal	Low	Moderate	N/A	Low-Moderate
Danucalov et al. (2013)	Low	Low	Minimal	Minimal	Moderate	Moderate	Low-Moderate
Davis et al. (2004)	Low	Minimal	Moderate	Minimal	Minimal	Low	Low
de Vugt et al. (2005)	Low	Low	Moderate	Minimal	Low	N/A	Low-Moderate
de Vugt et al. (2006)	Moderate	Low	Minimal	Minimal	Low	Moderate	Low-Moderate
Epel et al. (2010)	Low	Low	Minimal	Minimal	Moderate	Minimal	Low
Esterling et al. (1994)	Low	Low	Minimal	Minimal	Low	N/A	Low
Esterling et al. (1996)	Low	Low	Minimal	Minimal	Low	N/A	Low
Fonareva et al. (2011)	Low	High	Moderate	Minimal	Moderate	N/A	Moderate
Gallagher-Thompson et al. (2006)	Minimal	Low	Moderate	Minimal	Moderate	N/A	Low-Moderate
Garand et al. (2002)	Low	Low	Minimal	Minimal	Moderate	Low	Low
Glaser & Kiecolt (1997)	Moderate	Low	Minimal	Minimal	Low	N/A	Low
Glaser et al. (1998)	Moderate	Low	High	Minimal	Moderate	N/A	Moderate

Glaser et al. (2000)	Low	Low	High	Minimal	Moderate	N/A	Low-Moderate
Glaser et al. (2001)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Gouin et al. (2012)	Low	Low	Moderate	Minimal	Moderate	N/A	Low-Moderate
Graham et al. (2006)	Low	Low	Moderate	Minimal	Low	N/A	Low-Moderate
Grant et al. (2003)	Low	Low	Minimal	Minimal	Low	Low	Low
Hadjiconstantinou et al. (2001)	Low	Low	Moderate	Minimal	Low	N/A	Low-Moderate
Harmell et al. (2011)	Low	Low	Minimal	Minimal	Low	N/A	Low
Ho et al. (2014)	Low	Low	Moderate	Minimal	Moderate	N/A	Low-Moderate
Holland et al. (2010)	Minimal	Low	Minimal	Unclear (Moderate)	Low	Low	Low
Holland et al. (2011)	Low	Low	Minimal	Minimal	Moderate	Moderate	Low-Moderate
Innes et al. (2012)	Moderate	High	Moderate	High	Moderate	Low	Moderate-High
Irwin et al. (1991)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate

Irwin et al. (1997)	Low	Low	Minimal	Minimal	Low	N/A	Low
Irwin et al. (2013)	Moderate	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Jeckel et al. (2010)	Low	Low	Minimal	Minimal	Low	N/A	Low
Kiecolt-Glaser et al. (1991)	Moderate	Low	Minimal	Minimal	Low	Moderate	Low-Moderate
Kiecolt-Glaser et al. (1995)	Low	Low	Minimal	Minimal	Low	N/A	Low
Kiecolt-Glaser et al. (1996)	Moderate	Low	Minimal	Minimal	Low	Moderate	Low-Moderate
Kiecolt-Glaser et al. (2003)	Low	Low	Moderate	Minimal	Low	Unclear (moderate)	Low-Moderate
Kiecolt-Glaser et al. (2011)	Minimal	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Kim et al. (2007)	Moderate	Minimal	Minimal	Minimal	Low	N/A	Low
Kim et al. (2011)	High	Low	Moderate	Low	High	N/A	Moderate-High
King et al. (2002a)	Low	Low	Minimal	Minimal	Low	N/A	Low
King et al. (2002b)	Low	Low	Moderate	Minimal	Low	Low	Low-Moderate
Klein et al. (2014)	Minimal	Low	Minimal	Minimal	Low	Minimal	Minimal

Knight & McCallum (1998)	Low	High	Minimal	Minimal	Low	N/A	Low-Moderate
Knight et al. (2007)	Minimal	Low	Minimal	Minimal	Moderate	N/A	Low
Kring et al. (2010)	Low	High	Moderate	Minimal	Low	N/A	Low-Moderate
Lavretsky et al. (2013)	Low	Low	Moderate	Minimal	Low	Moderate	Low-Moderate
Leach et al. (2015)	Low	Low	Moderate	Minimal	Moderate	Minimal	Low-Moderate
Leggett et al. (2014)	Moderate	Low	High	Minimal	Moderate	Minimal	Moderate
Li et al. (2007)	Moderate	High	Minimal	Minimal	Low	Moderate	Low-Moderate
Lutgendorf et al. (1999)	Low	High	Moderate	Minimal	Moderate	N/A	Moderate
McCallum et al. (2006)	Low	Low	Moderate	Low	Moderate	N/A	Low-Moderate
McKenzie et al. (2013)	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate
Malarkey et al. (1996)	Moderate	High	Minimal	Low	Moderate	N/A	Moderate
Mausbach et al. (2005)	Moderate	High	Minimal	Minimal	Low	N/A	Low-Moderate
Mausbach et al. (2006)	Moderate	High	Minimal	Minimal	Moderate	N/A	Low-Moderate

Mausbach et al. (2007a)	Low	High	Moderate	Low	Moderate	High	Moderate
Mausbach et al. (2007b)	Moderate	High	Minimal	Minimal	Low	N/A	Low-Moderate
Mausbach et al. (2007c)	Low	Low	Minimal	Minimal	Low	Moderate	Low
Mausbach et al. (2008)	Low	Minimal	Minimal	Minimal	Low	High	Low-Moderate
Mausbach et al. (2010)	Moderate	Low	Minimal	Minimal	Low	N/A	Low
Mausbach et al. (2012)	Low	Low	Minimal	Minimal	Low	High	Low
Merritt et al. (2011)	Minimal	Minimal	Moderate	Minimal	Moderate	N/A	Low
Merritt & McCallum (2013)	Minimal	Minimal	Minimal	Minimal	Low	N/A	Minimal
Mills et al. (1997)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Mills et al. (2004)	Low	Low	Minimal	Moderate	Moderate	Moderate	Low-Moderate
Mills et al. (2009)	Low	High	Minimal	Minimal	Low	N/A	Low-Moderate
Mills & Yu (1999)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Moore et al. (2013)	Low	Minimal	Minimal	Minimal	Low	Moderate	Low
Neri et al. (2007)	Moderate	Low	High	High	Low	N/A	Moderate-High

Oken et al. (2010)	Moderate	Low	Minimal	Moderate	Moderate	N/A	Low-Moderate
Oken et al. (2011)	Low	Low	Moderate	Minimal	Low	N/A	Low-Moderate
Palma et al. (2011)	Low	Low	Minimal	Low	Moderate	N/A	Low-Moderate
Pomykala et al. (2012)	Low	Low	Minimal	Minimal	Low	Low	Low
Redwine et al. (2004)	Moderate	Low	Minimal	Minimal	Moderate	N/A	Low-Moderate
Reese et al. (1994)	Minimal	Low	Moderate	Minimal	Low	N/A	Low
Roepke et al. (2008)	Moderate	Low	Moderate	Minimal	Low	N/A	Low-Moderate
Roepke et al. (2011a)	Low	Low	Minimal	Minimal	Low	N/A	Low
Roepke et al. (2011b)	Low	Low	Moderate	Minimal	Low	N/A	Low-Moderate
Roepke et al. (2012)	Low	Low	Minimal	Minimal	Low	N/A	Low
Sakurai et al. (2015)	Low	Low	Moderate	Minimal	Moderate	Minimal	Low-Moderate
Sarabia-Cobo et al. (2015)	Low	Low	Moderate	High	Minimal	Minimal	Low-Moderate

Scanlan et al. (1998)	Low	Low	Minimal	Minimal	Moderate	Moderate	Low-Moderate
Scanlon et al. (2001)	Low	Low	Minimal	Minimal	Moderate	Low	Low
Schwartz et al. (2013)	Moderate	Low	Moderate	Minimal	Moderate	N/A	Low-Moderate
Segerstorm et al. (2008)	Low	Low	Moderate	Low	Moderate	Moderate	Moderate
Shaw et al. (2003)	Low	Low	Moderate	Minimal	Moderate	Low	Low-Moderate
Shaw et al. (1999)	Low	Minimal	Moderate	Minimal	Moderate	Low	Low-Moderate
Stalder et al. (2014)	Low	Low	Minimal	Minimal	Low	N/A	Low
Tarrier et al. (2002)	Moderate	Minimal	Minimal	Low	Low	N/A	Low
Thompson et al. (2004)	Moderate	Low	Minimal	High	Low	N/A	Low-Moderate
Tomiyama et al. (2012)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Uchino et al. (1992)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Uchino et al. (1994)	Low	Low	Moderate	Minimal	Moderate	Moderate	Low-Moderate
Vedhara et al. (1999)	Low	Low	Minimal	High	Moderate	Unclear (moderate)	Moderate

Vedhara et al. (2003)	Low	Low	Minimal	High	Moderate	Minimal	Low-Moderate
Vitaliano et al. (1995)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Vitaliano et al. (1996a)	Minimal	Low	Moderate	Minimal	Low	Unclear (moderate)	Low-Moderate
Vitaliano et al. (1996b)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Vitaliano et al. (1996c)	Low	Low	Minimal	Minimal	Moderate	N/A	Low
Vitaliano et al. (1998a)	Low	Low	Minimal	Minimal	Low	Minimal	Low
Vitaliano et al. (1998b)	Low	Low	Minimal	Minimal	Low	Low	Low
Vitaliano et al. (2001)	Low	High	Moderate	Minimal	Moderate	Minimal	Low-Moderate
Vitaliano et al. (2002)	Low	Minimal	Moderate	Minimal	Moderate	Low	Low-Moderate
Vitaliano et al. (2005)	Moderate	High	Minimal	Minimal	Moderate	Low	
Vitaliano et al. (2007)	Moderate	Low	Minimal	Minimal	Moderate	Minimal	
Vitaliano et al. (2009)	Low	Low	Minimal	Minimal	Low	Minimal	Low
Von Känel, et al. (2001)	Moderate	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Von Känel, et al. (2003)	Moderate	High	Minimal	Minimal	Moderate	N/A	Low-Moderate

Von Känel, et al. (2005)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Von Känel et al. (2006a)	Low	High	Moderate	Minimal	Moderate	N/A	Moderate
Von Känel et al. (2006b)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Von Känel, et al. (2010a)	Low	High	Minimal	Minimal	Moderate	N/A	Low-Moderate
Von Känel, et al. (2010b)	Moderate	Low	Moderate	Minimal	Low	Moderate	Low-Moderate
Von Känel, et al. (2011a)	Low	Low	Moderate	Minimal	Low	N/A	Low-Moderate
Von Känel, et al. (2011b)	Low	Low	Moderate	Minimal	Low	N/A	Low-Moderate
Von Känel, et al. (2012a)	Low	Low	Minimal	Minimal	Low	N/A	Low
Von Känel, et al. (2012b)	Low	Low	Moderate	Minimal	Low	Low	Low-Moderate
Von Känel, et al. (2012c)	Low	Low	Moderate	Minimal	Low	Minimal	Low
Von Känel, et al. (2014)	Moderate	Low	Moderate	Minimal	Moderate	Unclear (moderate)	Moderate
Wahbeh et al. (2008)	Low	High	Moderate	Minimal	Moderate	N/A	Moderate

Wilkins et al. (1999)	High	High	High	Minimal	Moderate	Moderate	Moderate-High
Wilcox et al. (2005)	Moderate	Minimal	Minimal	Minimal	Moderate	N/A	Low
Williams et al. (2010)	Moderate	Low	Moderate	High	Moderate	Unclear	Moderate-High
Wu et al. (1999)	Moderate	High	Minimal	Low	Moderate	Low	Moderate
Zarit et al. (2014)	Minimal	Low	Minimal	Low	Low	N/A	Low
Zhang et al. (2001)	Low	Low	Minimal	Low	Moderate	Unclear (moderate)	Low-Moderate
Zhang et al. (2006)	Low	High	Minimal	Minimal	Moderate	Unclear (moderate)	Low-Moderate