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A Randomized Clinical Trial of Behavioral Activation (BA) Therapy for Improving Psychological and Physical Health in Dementia Caregivers: Results of the Pleasant Events Program (PEP)

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Abstract

Dementia caregiving is associated with elevations in depressive symptoms and increased risk for cardiovascular diseases (CVD). This study evaluated the efficacy of the Pleasant Events Program (PEP), a 6-week Behavioral Activation intervention designed to reduce CVD risk and depressive symptoms in caregivers. One hundred dementia family caregivers were randomized to either the 6-week PEP intervention (N=49) or a time-equivalent Information-Support (IS) control condition (N=51). Assessments were completed pre- and post-intervention and at 1-year follow-up. Biological assessments included CVD risk markers Interleukin-6 (IL-6) and D-dimer. Psychosocial outcomes included depressive symptoms, positive affect, and negative affect. Participants receiving the PEP intervention had significantly greater reductions in IL-6 ($p=.040$), depressive symptoms ($p=.039$), and negative affect ($p=.021$) from pre- to post-treatment. For IL-6, clinically significant improvement was observed in 20.0% of PEP participants and 6.5% of IS participants. For depressive symptoms, clinically significant improvement was found for 32.7% of PEP vs 11.8% of IS participants. Group differences in change from baseline to 1-year follow-up were non-significant for all outcomes. The PEP program decreased depression and improved a measure of physiological health in older dementia caregivers. Future research should examine the efficacy of PEP for improving other CVD biomarkers and seek to sustain the intervention's effects.

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Keywords

Depression; Cardiovascular Disease; Alzheimer's Disease; Intervention; Treatment

INTRODUCTION

There is accumulating evidence that caregiving is a risk factor for the development of cardiovascular disease (CVD). For example, in a longitudinal study of over 8,000 U.S. adults aged 50 and over, caregivers were found to be at 35% increased risk for developing CVD relative to non-caregivers, even after controlling for demographic and health risk factors (Capistrant, Moon, Berkman, & Glymour, 2012). A prospective study of over 50,000 U.S. women found that caregivers with high daily care responsibilities were at nearly twice the risk for developing coronary heart disease (CHD) relative to non-caregivers (Lee, Colditz, Berkman, & Kawachi, 2003). Male caregivers also appear to be at higher risk than non-caregivers for developing CHD (Vitaliano et al., 2002). Given the evidence for the potential impact of caregiving on health, it stands that interventions to reduce caregiving distress should reduce risk for CVD. However, despite evidence that caregiving interventions are effective for reducing psychological distress (Gallagher-Thompson & Coon, 2007; Pinquart & Sorensen, 2006), little is known regarding their efficacy for reducing CVD risk.

In addition to clinical endpoints such as a CVD diagnosis, several studies have identified greater physiologic changes relevant to an increased CVD risk in caregivers. Two such biomarkers of physiologic shift are plasma concentrations of D-dimer and Interleukin-6 (IL-6). D-dimer is an indicator of fibrin formation and its subsequent lysis and is a useful biomarker representing overall activation of the coagulation system (Adam, Key, & Greenberg, 2009; Lip & Lowe, 1995). High concentrations of D-dimer have been linked prospectively to onset of CHD (Danesh et al., 2001), and caregivers have been found to have significantly higher concentrations of D-dimer relative to non-caregivers (von Känel et al., 2005; von Kanel et al., 2006). IL-6 is one of many markers represented in the “inflammatory cascade” which is initiated during an immune response (Hansson, 2005). Patients post-myocardial infarction or with unstable angina show elevated levels of IL-6, with higher levels of IL-6 predicting worse prognosis (Biasucci et al., 1996; Lindahl, Toss, Siegbahn, Venge, & Wallentin, 2000). Prospectively, increased plasma IL-6 is also associated with future myocardial infarction in healthy men, after controlling for other CVD risk factors (Ridker, Rifai, Stampfer, & Hennekens, 2000), and increasing concentrations of IL-6 have been associated with both nonfatal myocardial infarction and fatal CHD in longitudinal studies of population-based cohorts (Danesh et al., 2008). Notably, higher concentrations of IL-6 raise CHD risk, in some studies more than the related biomarkers C-reactive protein (CRP) and fibrinogen (Luc et al., 2003). Caregiving stress has been linked to increased IL-6 (Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012; von Kanel et al., 2006), particularly in caregivers with low psychological resources (Mausbach, von Kanel, et al., 2011), and caregivers show accelerations in IL-6 concentrations over time relative to non-caregivers (Kiecolt-Glaser et al., 2003). Given their links to CVD risk and caregiving, D-dimer and IL-6 are reasonable biomarker outcomes when determining the efficacy of treatments for caregivers.

In addition to elevated CVD risk, caregivers experience significantly higher levels of depressive symptoms relative to non-caregivers (Mausbach, Chattillion, Roepke, Patterson, & Grant, 2013; Pinquart & Sørensen, 2003), with high prevalence of depressive disorders being a consistent finding in the literature (Cuijpers, 2005). Elevated depressive symptoms, even those not meeting criteria for clinical diagnosis, are problematic for caregivers because

they are among the strongest predictors of overall caregiver health (Pinquart & Sorensen, 2007) and increase the likelihood that caregivers will need to visit the hospital (Schubert et al., 2008). Depressive symptoms are also associated with various CVD outcomes including D-dimer (Dentino et al., 1999) and IL-6 (Dentino et al., 1999; Dowlati et al., 2010; Hiles, Baker, de Malmanche, & Attia, 2012b), and increasing symptoms of depression raise caregivers' risk for CVD onset (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007). Importantly, these associations between depression and medical comorbidity, including CVD, are mediated in part by activation of immuno-inflammatory systems, which leads to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Belmaker & Agam, 2008) and subsequent elevations in proinflammatory cytokines such as IL-6 and CRP (Dantzer & Kelley, 2007; Miller, Maletic, & Raison, 2009). In meta-analyses, depressive symptoms and clinical depression have been associated with increased levels of circulating IL-6 with a medium effect size (Dowlati et al., 2010; Hiles et al., 2012b). Moreover, clinically depressed individuals have demonstrated increased secretion of proinflammatory cytokines in response to acute and chronic psychological stress (Kiecolt-Glaser et al., 2003; Miller, Rohleder, Stetler, & Kirschbaum, 2005), and chronic cytokine elevations are linked with depression (Raison, Capuron, & Miller, 2006), with stronger associations observed with increasing depression severity (Howren, Lamkin, & Suls, 2009). Treatment of depression is also associated with reductions in IL-6 (Hiles, Baker, de Malmanche, & Attia, 2012a). However, the links between depressive symptoms and CVD extend beyond the aforementioned immuno-inflammatory pathways. An independent role of depression, as well as other psychosocial factors such as psychological distress, has been demonstrated in the pathogenesis of CVD, with physiological, genetic, and behavioral factors connecting depression with worse cardiovascular outcomes (Bivanco-Lima, de Souza Santos, Vannucchi, & de Almeida Ribeiro, 2013; Huffman, Celano, Beach, Motiwala, & Januzzi, 2013; Mulle & Vaccarino, 2013; Neylon et al., 2013). In addition to the mentioned increased inflammation, some of these depressive-related risk factors include decreased heart rate variability, endothelial dysfunction, platelet abnormalities, autonomic nervous system dysfunction, lower reduced engagement in health-promoting activities (e.g., higher tobacco use, sedentary lifestyle, poor diet, reduced medication adherence), and diabetes mellitus (Bivanco-Lima et al., 2013; Huffman et al., 2013).

Given the links between depression and adverse health outcomes, particularly CVD, it is not surprising that depressive symptoms are the most targeted outcome in clinical trials involving caregivers (Schulz et al., 2002). Treatments that effectively reduce depression in caregivers should theoretically reduce risk of CVD. The present study included physiologic assessment of CVD risk indicators (i.e., IL-6 and D-dimer) as study outcomes, which represents a step toward understanding whether psychosocial interventions for depression may actually impact caregivers' CV health.

Among existing caregiver intervention studies, Cognitive Behavioral Therapies (CBT) appear to have the strongest effects on depressive symptoms (Gallagher-Thompson & Coon, 2007; Pinquart & Sorensen, 2006), particularly when more sessions are provided (Pinquart & Sorensen, 2006). However, there have been no studies examining the efficacy of these interventions for reducing caregiver CVD risk. Given its effectiveness for reducing depressive symptoms (Gould, Coulson, & Howard, 2012), CBT likely has potential to reduce CVD risk in caregivers. Among its variants, Behavioral Activation (BA) is particularly attractive because strong effects can be observed in relatively few sessions (Armento, McNulty, & Hopko, 2012; Cuijpers, van Straten, & Warmerdam, 2007; Gawrysiak, Nicholas, & Hopko, 2009). This becomes particularly important when considering that existing efficacious interventions are rarely made available to caregivers within their communities (Birkel, Granberry, & Alston, 2010). Additionally, it is relatively easy to train providers in BA techniques, making it an appealing intervention with potential

to reduce depressive symptoms, improve CVD risk, and be easily implemented by community agencies. Indeed, Ekers and colleagues (2011) demonstrated that behavioral activation therapy can be successfully implemented by non-mental health specialists after only five days of training and one hour of clinical supervision.

The present study examined the efficacy of a brief BA intervention for reducing depressive symptoms and biomarkers of CVD risk (i.e., D-dimer and IL-6) in dementia caregivers. The intervention, termed the Pleasant Events Program (PEP), was adapted from the treatment manual developed by Lejuez, Hopko, and Hopko (2001) and was based on the behavioral principles originally proposed by Lewinsohn (Lewinsohn & Graf, 1973; Lewinsohn & Libet, 1972). Lewinsohn's model focuses on increasing the frequency and duration of engagement in pleasurable activities through the increase of response-contingent environmental reinforcement, which then theoretically results in improved positive affect and cognitions and reduced negative affect. It has also been demonstrated that while increased engagement in pleasant activities resulted in increased overall well-being in a non-clinical sample, those individuals experiencing considerable life stress or negative affect (as is often the case with AD caregivers) are the ones to obtain reductions in stress as a result of BA (Mausbach, Roepke, Depp, Patterson, & Grant, 2009; Reich & Zautra, 1981). Among caregivers, engagement in pleasant events is often limited due to real or perceived restrictions to recreational and social events as a function of their caregiving role (Mausbach, Chattillion, et al., 2011; Mausbach, Patterson, & Grant, 2008; Williamson & Shaffer, 2000). Given that BA is an evidence-based treatment for depression and depressive symptoms are associated with CVD risk (Mausbach et al., 2007), we hypothesized the following:

1. Caregivers receiving the PEP intervention would demonstrate significant reductions in physiological CVD risk indicators (i.e., D-dimer and IL-6), relative to an Information and Support (IS) control condition.
2. Relative to caregivers in the IS condition, those receiving the PEP intervention would experience significant decreases in depressive symptoms and negative affect (NA), as well as significant increases in positive affect (PA).

Baseline characteristics of the caregivers, including hours spent caregivers, social support, and care recipient cognitive and functional impairment, were assessed and considered as possible confounding variables. Further, to explore to relative effectiveness of PEP over the IS condition, we calculated the Number Needed to Treat (NNT), an index with which to compare the benefits and risks of a therapeutic approach (Laupacis, Sackett, & Roberts, 1988). The NNT allowed our findings to be considered from both an efficacy point of view as well as in terms of relative clinical benefit.

METHODS

Participants

One hundred dementia caregivers were enrolled. Caregivers were eligible if they were aged 55 or older, and were providing at-home care for a care recipient (CR) with a physician-diagnosis of Alzheimer's disease (AD) or related dementia. Caregivers were excluded if they (a) were receiving beta-blocking medications at enrollment, (b) were receiving treatment with Anticoagulant medications, (c) had severe hypertension (>200/120 mmHg), (d) were diagnosed with a terminal illness with a life expectancy of less than 6 months, (e) were enrolled in another intervention study, or (f) were currently or had recently (i.e., during the prior 12 months) received behavioral or cognitive psychotherapy. Caregivers were not excluded if they received other forms of therapy such as support groups, as these are commonly attended by caregivers. Caregivers were recruited via referrals from the UCSD Alzheimer's Disease Research Center (ADRC) and the UCSD Alzheimer's Caregiver study,

via presentations at local support groups and health fairs, and from advertisements with local agencies serving caregivers.

The sample size calculation for this study was based on a meta-analysis of the efficacy of CBT interventions for reducing depressive symptoms in caregivers (Pinquart & Sorensen, 2006), which reported a mean effect size of 0.70 favoring CBT. With 90% power and 0.05 significance, we needed 44 participants in each treatment condition. Given the brevity of the interventions, we estimated a 12% attrition rate, requiring enrollment of 50 participants per condition.

Procedure

The study protocol was approved by the UCSD Institutional Review Board (IRB). After providing informed consent, caregivers meeting enrollment criteria were assessed in their homes. A trained research assistant interviewed participants by administering a series of questionnaires assessing psychosocial variables (e.g., depressive symptoms, positive and negative affect) and collecting demographic information, after which a research nurse collected blood samples to be assayed for biomarker outcomes. A computerized random number generator was used to randomize caregivers to either the PEP or IS condition. After treatment completion (i.e., post-therapy) and again at 1-year, caregivers underwent a complete psychosocial and physiologic assessment. Throughout the trial assessors and the research nurse were blind to randomization condition. Participants were compensated \$40 for each completed assessment (maximum = \$120), but not for therapy participation.

All therapy sessions were provided by two Master's level clinicians. One of the clinicians had a Master's in Clinical Psychology and the other clinician had a Master's in Marriage and Family Therapy. Each clinician provided therapy for approximately half of the participants. Therapist 1 provided therapy to 56 participants (28 IS and 28 PEP); and Therapist 2 provided therapy to 44 participants (23 IS and 21 PEP). The PI (BTM) provided training on the specific study procedures. Therapy sessions were audio recorded at random and were reviewed for adherence to the protocol.

Participants in both conditions received four in-home therapy sessions each lasting approximately one hour. Following the four in-home sessions, caregivers in both conditions received 2 weekly phone sessions conducted by the same therapist who had conducted the in-home sessions. Duration of phone sessions was determined by the caregiver and varied from 15 minutes to one hour. Participants in both conditions were given a treatment manual. The manuals included chapter information and various worksheets to be completed during or between sessions.

PEP Intervention—The PEP intervention was adapted from the published treatment manual by Lejuez and colleagues (Lejuez et al., 2001) and all participants were provided with a treatment manual during the first session¹. The manual contained four chapters, with one chapter covered per treatment session. The key components of the four sessions were: (1) education on how to monitor use of time, particularly time spent in leisure activities, (2) identification of leisure activities enjoyed by the caregiver, (3) development of an activity hierarchy to help caregivers prioritize their activities, and (4) scheduling/participating in selected leisure activities and tracking of moods. In selecting and engaging activities, caregivers were encouraged to choose activities they felt comfortable performing in the context of their ongoing caregiving duties. Caregivers were never encouraged to perform

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¹Send requests for the PEP manual to Brent T. Mausbach, bmausbach@ucsd.edu.

activities that would leave their care recipient unattended or in danger. A summary of the content of each session is provided in Table 1.

IS Control Condition—Participants in the IS control condition were provided with a resource manual consisting of topics commonly covered in support groups or information packets provided by community agencies. Topics included problem-solving and communication skills, cognitive reframing, and behavioral management (e.g., teaching caregivers how to manage problem-behaviors of their spouses), self-care help, caregiver fact sheets on a range of social and mental health issues, placement information, financial and legal issues, and lists of local organizations and community resources available. Less structured than the PEP condition, each IS session allowed caregivers to select which issue(s) from the resource manual they would like to discuss, if any, and the therapist covered the material based on the caregivers' needs. When requested by the caregiver, supportive psychotherapy was also provided.

Measures

Demographic Characteristics—These included age, sex, level of formal education, monthly household income, years providing care, and hours of care provided per day.

D-dimer and Interleukin-6—Blood was collected by a research nurse in the caregivers' homes through a 22-gauge forearm catheter after a 20 minute rest. Blood for IL-6 was dispensed in EDTA tubes and spun at 3000g for 10 minutes at 4–8 °C. Blood for D-dimer was dispensed into polypropylene tubes with 3.8% sodium citrate and spun at 1600g for 10 minutes at room temperature. Obtained plasma was stored at –80°C until analyzed. Plasma IL-6 (Meso Scale Discovery, Gaithersburg, MD) and D-dimer (Asserachrom Stago, Asnières, France) were determined via high-sensitive enzyme-linked immunosorbent assays. Intra- and inter-assay coefficients of variation were <5% for both IL-6 and D-dimer, sensitivities were excellent.

Depressive Symptoms—These were assessed using the short form of the Center for Epidemiologic Studies Depression (CESD) scale (Andresen, Malmgren, Carter, & Patrick, 1994), which contains 10 items from the original 20-item scale and has been validated in both older adults and caregivers (Andresen et al., 1994). Caregivers reported their experience of depressive symptoms over the past week with responses ranging from 0 = “none of the time” to 3 = “most of the time.” The sum of the items creates an overall score reflecting current depressive symptoms. Relative to the full CESD, scores of 8 or higher on the CESD-brief are indicative of clinically meaningful levels of depressive symptoms. Coefficient alpha for the present sample was .71.

Positive and Negative Affect—Caregivers completed the Positive and Negative Affect Schedule (PANAS), which is a 20-item scale consisting of mood adjectives (Watson, Clark, & Tellegen, 1988). Ten items assess positive affect (PA), such as “interested,” “strong,” and “inspired” and ten items measure Negative Affect (NA), such as “distressed,” “ashamed,” and “upset”. Participants rated each adjective based on how they felt over the past few weeks using a 5-point scale with responses ranging from 1 = “very slightly to not at all” to 5 = “extremely.” For this study, coefficient alpha was .94 for both the PA and NA scales.

Social Support—We used the 8-item Social Support scale developed by Pearlin et al. (1990) to assess the help and support caregivers' received from friends and relatives. Caregivers responded on a 4-point Likert scale (1 = “strongly disagree” to 4 = “strongly agree”) to statements such as, “The people close to you let you know they care about you.” For the present study, coefficient alpha for the Social Support scale was .76.

Care Recipient Cognitive and Functional Impairment—The Clinical Dementia Rating (CDR) scale (Morris, 1993) was used to assess the dementia severity of the care recipient. Level of functioning was reported by the caregivers in 6 behavioral and cognitive domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. A total score was created based on scores from the 6 domains, with higher scores indicating more severe dementia.

To assess care recipient functional impairment, caregivers rated their care recipients on 15 activities of daily living (ADLs; e.g., eating, bathing, toileting)(Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) and instrumental activities of daily living (IADLs; e.g., handling money, taking medications)(Lawton & Brody, 1969). ADLs/IADLs dependence were rated on a 4-point Likert scale ranging from 1 = “*not at all*” to 4 = “*completely*.” Scores were summed to create total ADL/IADL dependence scores. Coefficient alpha of this scale was .91.

Program evaluation—To assess participant’s subjective perceptions of the two treatment conditions, participants completed a program evaluation at their 6-week follow-up. Items of this evaluation included: “How satisfied were you with the therapist’s personal style?”, “How satisfied were you with the duration of each weekly session/frequency of sessions/total number of sessions?”, “What was your overall satisfaction with the program?”, and “How likely are you to recommend this program to other caregivers?” Responses ranged from 4 = *very satisfied* to 1 = *not at all satisfied*.

Data Analysis

Data was analyzed using PASW version 18. An intent-to-treat approach was employed in all analyses, which included all 100 randomized participants. The primary psychological outcome was change on the CESD-Brief, whereas the primary physiologic outcome was change in D-dimer. Change on these outcomes was evaluated using mixed-models repeated measures analysis of variance with restricted maximum likelihood (REML) estimation. Treatment group (PEP vs. IS), assessment point (baseline, post-treatment, and 1-year follow-up), and their interaction were fixed effects. Subjects were treated as a random effect. The group-by- time interaction was the fixed effect of interest. Planned contrasts were conducted to examine changes from baseline to each of our two outcome time-points (i.e., post-treatment and 1-year follow-up). Secondary outcome analyses were conducted to evaluate change in IL-6, PA, and NA using the same procedure described above. For all analyses, baseline levels of the outcome and social support were entered as covariates.

We calculated three effect sizes for all primary and secondary outcomes. The first effect size was Cohen’s d, which was calculated using the formula described by Feingold (Feingold, 2009). Second, as an indicator of clinical significance we calculated the number-needed-to-treat (NNT) with Newcombe-Wilson 95% confidence intervals using the formulae provided by Bender (Bender, 2001) and Newcombe (Newcombe, 1998). Clinical significance was defined as at least a 50% reduction from baseline as per the following formula provided by Furukawa (Furukawa & Leucht, 2011): $C\% = (C_0 - C_{pLOCF}) * 100 / C_0$, where C_0 and C_p are the CESD scores from baseline and post-treatment, respectively, and LOCF indicating last observation carried forward as a conservative method for assuming participants without follow-up data did not change from baseline. A 50% reduction has been used to define clinically meaningful reduction in a number of clinical trials (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Hopko et al., 2011; Richards & Suckling, 2009; Titov et al., 2010; Unutzer et al., 2002). Finally, we calculated the reliable change index (RCI) as described by Jacobson and Truax (1991). The RCI is a measure of clinically significant

change based on pre-treatment and post-treatment means and standard deviations as well as the test-retest reliability of the outcome measure in question.

RESULTS

Participant Characteristics

Figure 1 shows the flow of participants through the trial. A total of 14 participants did not complete the post-treatment assessment, 6 (12.2%) in the PEP condition and 8 (15.7%) in the IS condition ($\chi^2 = 0.25$, $df = 1$, $p = .62$). A total of 16 participants (32.7%) in the PEP condition and 19 in the IS condition (37.3%) did not complete the 1-year follow-up ($\chi^2 = 0.23$, $df = 1$, $p = .63$). For both conditions, placement or death of the CR was the primary reason for not completing the follow-up (PEP = 8, IS = 12; $\chi^2 = 0.81$, $df = 1$, $p = .37$).

As seen in Table 2, caregivers in both treatment conditions did not significantly differ on any demographic or caregiving variables. Further, no baseline characteristics were associated with dropout over the course of the trial, including CG age ($t = 0.15$, $df = 98$, $p = .88$), sex ($\chi^2 = 0.06$, $df = 1$, $p = .81$), years of education ($t = -1.27$, $df = 98$, $p = .21$), depressive symptoms ($t = -0.37$, $df = 98$, $p = .72$), PA ($t = -0.74$, $df = 98$, $p = .46$), NA ($t = -0.50$, $df = 98$, $p = .46$), D-dimer ($t = -0.92$, $df = 90$, $p = .36$), or IL-6 ($t = 1.05$, $df = 89$, $p = .30$). In addition, no significant differences were observed between the two treatment conditions on any baseline variables (see Table 2), therefore none of these variables were included as covariates in the analyses.

Changes in Physiologic Outcomes

Estimated means and standard errors for the PEP and IS conditions across the three assessments are presented in Table 3. Contrast estimates for change from pre-treatment to each of the follow-up assessments are presented in Table 4. When examining within-subjects contrasts for D-dimer, no significant difference between the PEP and IS conditions was observed at the end of treatment ($t = -0.39$, $df = 146.04$; $p = .70$) or at the 1-year follow-up ($t = -1.40$, $df = 160.49$, $p = .16$). When examining clinical significance, 1 of 45 participants (2.2%) in the IS condition and 3 of 47 in the PEP condition (6.4%) showed at least 50% reduction in D-dimer from pre-treatment to post-treatment, with NNT = 23.8 and small to medium effect size ($d = 0.33$) between baseline and 1-yr follow-up.

When examining change in IL-6, a significant difference between the PEP and IS conditions was observed at the end of treatment ($t = -2.07$, $df = 145.80$; $p = .040$), but not at the 1-year follow-up ($t = 0.05$, $df = 161.52$, $p = .96$). Out of 45 participants in the PEP condition, 9 demonstrated a 50% reduction in IL-6 levels (20.0%), compared to 3 of 46 participants in the IS condition (6.5%). This equated to a NNT of 7.4. Based on RCI cutoffs, 8.6% of the PEP participants demonstrated clinically significant change compared to none of the IS participants.

Improvement in Psychological Symptoms

Our primary psychological outcome was depressive symptoms. When examining our a priori within-subjects contrasts, a significant difference between the PEP and IS conditions was observed at the end of treatment ($t = -2.08$, $df = 165.26$; $p = .039$), but not at the 1-year follow-up ($t = -1.24$, $df = 178.99$, $p = .22$). When examining clinical significance, 6 of 51 participants (11.8%) in the IS condition and 16 of 49 in the PEP condition (32.7%) showed at least 50% reduction in depressive symptoms from pre-treatment to post-treatment, with NNT = 4.8 (95% CI = 2.8–21.8). As an additional analysis, we compared the mean decrease in CESD scores (PEP vs IS) for the 22 participants who achieved a 50% reduction in symptoms. Among the 6 participants in the IS group, mean change on the CESD was 6.67

(SD = 3.20), compared to 9.19 (SD = 4.71) for participants in the PEP condition ($t = 1.20$, $df = 20$, $p = .243$). Based on RCI cutoffs, 27.9% of the PEP participants demonstrated clinically significant change compared to 9.3% of the IS participants. For 1-year follow-up, 7 (13.7%) participants in the IS condition and 12 in the PEP condition (24.5%) showed a 50% reduction (from baseline scores) in depressive symptoms (NNT = 9.3).

Our secondary psychological outcomes were PA and NA. For PA, within-group contrasts indicated no differences between treatment conditions at post-treatment ($t = 1.11$, $df = 166.76$, $p = .27$) or 1-year follow-up ($t = 0.46$, $df = 179.09$, $p = .65$). For NA, a significant difference between the PEP and IS conditions was observed at the end of treatment ($t = -2.34$, $df = 158.12$; $p = .021$), but not at the 1-year follow-up ($t = -0.79$, $df = 175.35$, $p = .43$). Based on RCI cutoffs, 9.3% of the PEP participants demonstrated clinically significant change from baseline to post-treatment compared to 2.4% of the IS participants.

Program Evaluation Results

Program evaluations were obtained from a total of 40 PEP participants and 40 IS participants. Caregivers in the PEP (mean $\pm$ SD = 3.85 ± 0.33) and IS conditions (3.85 ± 0.40) did not significantly differ in terms of satisfaction with their therapist ($t = 0.00$, $df = 78$, $p > .99$), satisfaction with the provided written material (PEP = 3.60 ± 0.78 , IS = 3.73 ± 0.64 ; $t = 0.44$, $df = 78$, $p = 0.44$), overall satisfaction with the program (PEP = 3.64 ± 0.71 , IS = 3.73 ± 0.60 ; $t = 0.57$, $df = 77$, $p = .57$), or likelihood of recommending the program to other caregivers (PEP = 3.63 ± 0.63 , IS = 3.78 ± 0.48 ; $t = 1.13$, $df = 76$, $p = .26$). Caregivers in the PEP condition were slightly, but not significantly, less satisfied with the number of treatment sessions provided (PEP = 3.58 ± 0.55 , IS = 3.75 ± 0.49 ; $t = 1.50$, $df = 78$, $p = .14$).

DISCUSSION

This study examined the efficacy of PEP, a brief BA therapy for improving psychological health and reducing CVD risk in elderly dementia caregivers. Results indicated that CVD risk, as measured by the inflammatory marker IL-6, was significantly lowered at post-treatment in caregivers in the PEP intervention compared with caregivers receiving the IS control intervention. Additionally, we found a NNT of 5.9 for change in IL-6 from baseline to post-treatment, indicating that out of every six caregivers treated with PEP, one caregiver would demonstrate a clinically meaningful reduction in inflammation compared with the IS condition. Differences between the PEP and IS groups were not observed with regard to change in coagulation (D-dimer); however, D-dimer appeared slightly reduced in both conditions from pre- to post-treatment. Although both D-dimer and IL-6 are associated with CVD risk, IL-6 may be more strongly linked with depression, given that inflammation is regarded as a common mechanism of disease in both depression and CVD (Dowlati et al., 2010; Hansson, 2005; Hiles et al., 2012b; Miller et al., 2009). This mechanistic overlap may help explain why changes in depression resulting from our intervention were paralleled by changes in IL-6 but not D-dimer. The findings of our intervention are especially encouraging given that the control condition was not a “true control,” but was an active information-support psychotherapy intervention. The active nature of the “control” condition could also help explain why both the PEP and IS groups showed reduced D-dimer levels, indicating that information and supportive psychotherapy had a slight (though non-significant) benefit for this coagulation marker.

The results of this study expand upon prior intervention research demonstrating that the provision of respite to dementia caregivers reduces sympathetic nervous system (SNS) activation, namely plasma epinephrine levels, over a brief intervention period (Grant et al., 2003). Overall, the present study provides preliminary evidence regarding the potential health benefits of psychological interventions for caregivers by examining additional and

potentially more meaningful biomarkers of CVD risk. For example, IL-6 has emerged as a useful clinical marker of CVD risk, given its ability to be easily detected in peripheral circulation and the great deal of evidence associating IL-6 with cardiovascular morbidity and mortality (Hansson, 2005). Given the established links between depression and medical comorbidity, including CVD, relatively few studies have directly examined whether interventions designed to improve depression also result in changes in physiologic measures of CVD risk or CV health. We believe that inclusion of physiologic assessment in this study represents a novel approach to assessing the efficacy of caregiver depression interventions. We encourage future caregiver intervention research to assess for changes in physiologic health outcomes, including biomarkers of an increased CVD risk, in order to more directly examine whether psychosocial interventions can impact caregivers' physical as well as mental well-being.

In addition to measuring health outcomes related to CVD risk, we measured changes in depressive symptoms and mood. Participation in the PEP intervention resulted in significantly lower depressive symptoms and negative affect at post-treatment and 12 month follow-ups. When examining clinically meaningful outcomes, participation in the PEP intervention was associated with greater symptom reduction than participation in the IS condition, with NNT at post treatment and 1-year follow-up of 4.8 and 9.3, respectively. However, when comparing mean change in depressive symptoms over 1-year, PEP and IS did not significantly differ. Failure to find sustained group differences at 1-year follow-up may have resulted from the lack of continued accountability, encouragement, and problem-solving from a therapist. Future caregiver intervention studies may benefit from including additional in-person behavioral activation therapy sessions (i.e., repeats of sessions 3 and 4 of PEP), additional follow-up phone calls, or monthly or quarterly booster sessions, focused on continued behavioral activation throughout the post-treatment follow-up period.

Our results compare favorably to other interventions designed to reduce caregiver distress. Specifically, meta-analyses suggest Cohen's *d* effect sizes range from 0.24 (Pinquart & Sorensen, 2006) to 0.31 (Brodaty, Green, & Koschera, 2003) for caregiver interventions targeting psychological morbidity, with psychoeducational interventions and CBT having the strongest effects. These meta-analyses further report that longer interventions (i.e., greater number of treatment sessions) produce the strongest effects on psychological morbidity. In contrast, our intervention is brief (lasting approximately 6 weeks) yet still achieved an effect size of 0.40 for pre- to post-treatment. Additionally, a main advantage of PEP over other caregiver interventions is the ease with which it can be implemented and disseminated. Therapists of all levels (e.g., individuals working in primary care, marriage and family therapists, social workers), can be easily trained to deliver the PEP intervention, and the brevity of the intervention allows for delivery in a variety of settings. Given the large percentage of caregivers who attend community support groups, these groups may be an ideal setting in which to implement this intervention. However, as previously noted, the addition of booster sessions after the initial brief intervention may help caregivers sustain improvement in mood over a longer follow-up period.

There are several limitations to this study. First, as this was a preliminary study, the sample size was relatively small which limited the ability to detect effects with narrow confidence intervals. A future larger trial with greater focus on maintenance of effects is needed to detect greater differences between the two treatments. Second, our design used an active control condition in which caregivers met and discussed caregiving issues with a counselor. Because of the active nature of the control group we were able to control for the effects of therapeutic contact on our outcomes, but doing so potentially limited the effect sizes of differences between groups, particularly at the 1-year follow-up. However, we note that a lack of differences at the 1-year follow-up did not appear to be due to the benefits of our

control group, but rather to the waning of effects of our PEP condition, particularly for affective outcomes. Additionally, thorough assessment of homework compliance during therapy was not conducted, and we did not conduct follow-up interviews asking participants whether they continued using strategies learned in either the PEP or IS condition after therapy was completed. However, because behavioral activation was the sole focus of the PEP condition, which was not utilized as a component of the IS condition, we expect this was the mechanism by which caregivers improved. Nonetheless, future studies would benefit from obtaining these data to help determine whether more sessions during the active treatment phase or booster sessions would be beneficial. Additionally, the sample size and composition was not powered to detect racial or ethnic differences among the participants. Caregivers were primarily Caucasian (90.0%), so it is unknown whether the results would generalize to other racial or ethnic groups. Other caregiver intervention studies, such as the multi-site REACH II trial (Belle et al., 2006), were powered to detect racial and ethnic differences. We encourage clinicians to weigh the advantages and disadvantages of different interventions for use with different racial and ethnic groups when evaluating treatment options. A third limitation is that we did not assess caregivers' use of anti-anxiety medications, which may include benzodiazepines and antidepressants, which might affect psychological and physiological outcomes assessed in our study. Future studies should account for the impact of these medications to better understand the direct impact of the PEP treatment on affective outcomes. Another limitation is that, although we believe the PEP intervention would perform equally well in a group setting, it was only tested on an individual level. Future research should directly examine PEP's efficacy in a group setting, such as caregiver support groups and hospital or community psychotherapy groups. Moreover, only family caregivers (i.e., spouses and children) were enrolled in this trial, and it is unknown whether PEP would reduce depression and CVD risk factors in non-familial caregivers (i.e., professional caregivers, neighbors, friends). Other limitations to this study include the following: 1) employment status of the caregivers was not assessed, and employment among caregivers may have implications for adherence to the treatments, 2) care recipients were not interviewed, and there is a possibility that some of the care recipients had a co-existing psychological disorder which may have increased caregiver distress; 3) duration of phone call sessions was not recorded, so it is unknown whether there were differences between the two groups. However, according to the therapists individual reports differences in the duration of phone calls varied as a function of the caregiver personality, not treatment condition; and 4) there was no formalized assessment of therapist competence and treatment adherence. However, a licensed psychologist (BTM) performed random reviews of recorded therapy sessions and met with each therapist for supervision on a weekly basis, so deviations from the treatment protocols were minimized.

Notwithstanding its limitations, depression and CVD risk remain significant problems in dementia caregivers (Mausbach et al., 2013; Mausbach et al., 2007), and developing interventions that can be delivered to caregivers within the constraints of their caregiving role presents a significant challenge. Our work demonstrates the potential of the PEP intervention for improving overall well-being in elderly familial dementia caregivers, including short-term improvement in inflammatory biomarkers of CVD risk. Factors that are most encouraging about the PEP intervention include its brevity, portability, and potential for possibly reducing CVD risk in addition to improving depressive symptoms. Although a larger trial demonstrating the reproducibility of these findings is needed, including information about PEP's efficacy for reducing other biomarkers of CVD risk, we believe dissemination of PEP within existing community programs (e.g., caregiver support groups), has the potential to improve the overall health and well-being of the rapidly growing population of dementia caregivers. Yet, adaptations may be needed to improve the long-term sustainability of the intervention's effects, such as including more sessions and/or the addition of boosters.

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Highlights

- We studied Behavioral Activation (BA) therapy for reducing depression and CVD risk
- Dementia caregivers were randomized to BA or information-support (IS) therapy
- BA therapy showed promise for reducing depression and IL-6, a biomarker of CVD risk
- This study is novel in showing efficacy of BA for psychological and physical health
- BA therapy is brief and straightforward, allowing for community implementation

CONSORT Flow Diagram

Figure 1.

Table 1**Session Order and Content of the PEP Treatment**

Session No.	Session Title	Summary of Contents	Homework
1	Recognizing Negative Moods and Creating a Healthy Environment	Overview of PEP; recognizing negative moods; creating a healthy environment	Completion of mood questionnaire; daily activity log; behavioral contract
2	Measuring Life Goals and Identifying Activities	Measuring life goals; life goals assessment; activity identification	Completion of mood questionnaire; activity difficulty assessment; activity hierarchy
3	Getting More PEP-Behavioral Activation	Creation of a Master Activity Log based on activity hierarchy; 2–3 behaviors selected from the Master Activity Log as goal for this week. Caregivers chose the number of times to engage in selected activities (e.g., four times) and the duration for each (e.g., 20 minutes each time)	Completion of mood questionnaire; weekly behavior checkout
4	Continuing to Get More PEP – Behavioral Activation	Modification of previous week's goals; problem-solving to overcome barriers to accomplishing goals; identification of new goals	Completion of mood questionnaire; weekly behavior checkout; activity level graph; positive and negative mood graphs
5–6	Continued Behavioral Activation and Maintaining Progress	Identification of new goals; long-term continued behavioral activation planning and problem-solving	Completion of mood questionnaires; weekly behavior checkouts; activity level graph; positive and negative mood graphs

Note. Sessions 1–4 were conducted in-person, while sessions 5–6 were conducted over the telephone.

Table 2

Baseline characteristics of the sample by treatment condition

	PEP (n = 49)	IS (n = 51)	2	t-score	p-value
<i>Caregiver Characteristics</i>					
Age (years), mean (SD)	70.86 (7.57)	71.33 (9.08)		-0.29	.777
Sex (female), n (%)	40 (81.6)	34 (66.7)	2.91		.088
Caucasian, n (%)	44 (89.8)	46 (90.2)	0.00		.947
Education (years), mean (SD)	15.16 (2.27)	15.10 (3.45)		0.11	.912
Years Caregiving, mean (SD)	5.42 (4.91)	3.95 (2.41)		1.90	.061
Taking Anti-depressant Medications, n (%)	18 (36.7%)	17 (33.3%)	0.13		.721
Hours Providing Care per Day, mean (SD)	8.22 (5.00)	8.02 (5.38)		0.20	.844
Social Support, mean (SD)	25.24 (3.69)	25.39 (4.16)		-0.19	.852
Attended support group in past month, n (%)	33 (67.3)	32* (64.0)		0.12	.726
<i>Care Recipient Characteristics</i>					
CR CDR Score, n (%)					
1	24 (49.0)	17 (33.3)	3.62		.163
2	24 (49.0)	30 (58.9)			
3	1 (2.0)	4 (7.8)			
CR ADL, mean (SD)	38.20 (8.95)	38.24 (10.46)		-0.02	.987

* One participant did not answer this question.

Table 3

Estimated mean scores for outcome measures for each intervention condition across measurement occasions.

Measure	Condition	Measurement Occasion					
		Pre-Intervention		Post-Intervention		1-year Follow-up	
		n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
D-dimer (ng/ml)	PEP	47	731.22 (39.08)	37	639.00 (44.54)	23	668.31 (55.70)
	IS	45	729.85 (39.89)	37	668.85 (44.82)	23	798.48 (56.83)
Interleukin-6 (pg/ml)							
	PEP	45	2.06 (0.45)	37	1.48 (0.51)	22	1.67 (0.66)
	IS	46	2.18 (0.45)	39	3.51 (0.51)	23	1.75 (0.63)
CESD-Brief							
	PEP	49	11.77 (0.54)	43	8.31 (0.58)	33	9.55 (0.66)
	IS	51	11.39 (0.53)	43	10.13 (0.58)	32	10.62 (0.68)
Positive Affect							
	PEP	49	31.14 (0.60)	43	32.65 (0.64)	33	31.42 (0.74)
	IS	51	31.47 (0.59)	42	31.70 (0.65)	32	31.17 (0.76)
Negative Affect							
	PEP	49	20.94 (0.59)	43	17.51 (0.63)	33	18.67 (0.73)
	IS	51	20.26 (0.58)	42	19.65 (0.64)	32	19.04 (0.75)

Table 4

Contrast estimates, 95% confidence intervals (CI), test of significance values, and effect size estimates of change from baseline to post-treatment and 1-year follow-up assessment between PEP and IS conditions.

Outcome	Statistic	Baseline to post-treatment	Baseline to 1-year follow-up	Cohen's d Baseline to post-treatment	Cohen's d Baseline to 1-year follow-up
D-dimer	Contrast Estimate	-.31.21	-.131.53	0.08	0.33
	95% CI	-191.46 to 129.04	-316.88 to 53.82		
	P-value	.701	.163		
IL-6	Contrast Estimate	-1.91	0.05	0.52	-0.01
	95% CI	-3.73 to -0.09	-2.08 to 2.18		
	P-value	.040	.964		
CESD-Brief	Contrast Estimate	-2.20	-1.44	0.42	0.28
	95% CI	-4.28 to -0.12	-3.74 to 0.85		
	P-value	.039	.216		
Positive Affect	Contrast Estimate	1.29	0.59	0.18	0.08
	95% CI	-1.00 to 3.30	-1.94 to 3.12		
	P-value	.268	.645		
Negative Affect	Contrast Estimate	-2.82	-1.04	0.41	0.15
	95% CI	-5.20 to -0.44	-3.65 to 1.57		
	P-value	.021	.433		

Note. For D-dimer, IL-6, CESD, and Negative Affect, negative contrast estimates indicate the PEP group showed greater improvement than the IS group.