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Research Article

Effects of Psychosocial Interventions and Caregiving Stress on Cardiovascular Biomarkers in Family Dementia Caregivers: The UCSD Pleasant Events Program (PEP) Randomized Controlled Trial

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Abstract

Background: This study examined whether biological mechanisms linking dementia caregiving with an increased risk of coronary heart disease can be modified by psychosocial interventions and which caregivers might benefit the most from an intervention.
Methods: Spousal dementia caregivers were randomized to 12-week treatment with either a behavioral activation intervention (ie, Pleasant Events Program [PEP]; n = 60), or an active control Information and Support (IS; n = 63) condition. Indicators of caregiving stress were assessed pretreatment and circulating cardiovascular biomarkers were measured pre- and posttreatment.
Results: There were no significant changes in biomarker levels from pre- to posttreatment both by treatment condition and across all caregivers. Regardless of the treatment condition, exploratory regression analysis revealed that caregivers were more likely to show significant decreases in C-reactive protein (CRP) and D-dimer when their spouse had severe functional impairment; in interleukin (IL)-6 and CRP when they had greater distress due to care recipient's problem behaviors; in tumor necrosis factor (TNF)-α when they had higher levels of negative affect; and in IL-6, CRP, TNF-α, and D-dimer when they had higher personal mastery. Within the PEP group, caregivers with higher negative affect and those with higher positive affect were more likely to show a reduction in von Willebrand factor and D-dimer, respectively. Within the IS group, caregivers whose spouse had severe functional impairment were more likely to show a decrease in IL-6.
Conclusions: Unlike the average caregiver, caregivers high in burden/distress and resources might benefit from psychosocial interventions to improve cardiovascular risk, although these observations need confirmation.

Keywords: Blood coagulation, Cardiovascular disease, Dementia caregiving, Inflammation, Psychosocial stress

Informal caregiving for a family member has been associated with an increased risk of cardiovascular disease, particularly incident coronary heart disease (CHD) (1–4). The risk of CHD is greater in caregivers experiencing higher levels of burden and distress compared to their less stressed counterparts (1,2,4). Inflammatory and prothrombotic changes might partially explain this link as they are key contributing factors to atherosclerosis (5,6) and acute coronary thrombosis (7,8). Meta-analyses demonstrated a direct association of circulating inflammatory and prothrombotic biomarkers, including C-reactive protein (CRP) (9), interleukin (IL)-6 (10), tumor necrosis

factor (TNF)-α (10), D-dimer (11), von Willebrand factor (VWF) (11), and plasminogen activator inhibitor (PAI)-1 (12), with incident CHD. Higher levels of CRP (13), IL-6 (14), TNF-α (15), and D-dimer (16), a marker of increased fibrin turnover, were found in dementia caregivers compared to noncaregiving controls. However, findings from the two most recent systematic reviews on negative effects of caregiving on biomarkers of immune function, inflammation and coagulation are mixed (17,18). For instance, meta-analysis showed no statistical difference in both IL-6 and CRP levels between caregivers and controls, although this analysis also included studies on caregivers for persons who are not afflicted by dementia (18).

Whereas dementia caregiver status in itself may not strongly affect biological processes detectable by circulating biomarkers, various facets of a stressful caregiving experience could have a greater impact. For instance, after adjustment for covariates, years caregiving (15), and daily stressors (13) were associated with higher CRP. Both dementia severity (19) and caregiver distress due to problem behaviors of the care recipient (20) were associated with higher D-dimer. In contrast, stress buffering resources like personal mastery or satisfaction with leisure activities, were associated with lower PAI-1 (21) and TNF-α (22), respectively. Such biomarker research helps to gain deeper insight into the pathogenic pathway leading from caregiver stress to coronary atherosclerosis and thrombosis.

Whether stress-reducing interventions improve caregivers' cardiovascular health has rarely been investigated (17,23) with only one previous study from our group targeting biomarkers of CHD risk (24). In that trial, we showed greater reduction in IL-6, but similar D-dimer levels, in dementia caregivers who underwent a 6-week Pleasant Events Program (PEP) intervention, targeting participation in pleasurable activities, compared to caregivers having received Information and Support (IS) (24). The present study was performed in a different sample of caregivers with the primary aim of extending these previous findings. We explored the effects of a 12-week treatment with PEP versus time-equivalent IS on changes in IL-6 levels, as the primary outcome and on TNF-α, CRP, D-dimer, VWF, and PAI-1 levels as secondary outcomes. We hypothesized that PEP would result in significantly greater reduction of IL-6 and additional biomarkers compared to IS.

Personalized care can be fully realized only when contextual social and behavioral health determinants are investigated within interventions (25), bearing in mind that psychological treatments can also have adverse effects (26). Hence, the secondary aim of our study was to explore indicators of caregiving stress as predictors or moderators of biomarker responses to treatment. A predictor would affect biomarker responses equally for PEP and IS, whereas a moderator would affect the relative effect of PEP and IS on biomarker responses. This knowledge could inform clinicians as to whether a caregiver should be offered certain psychosocial interventions targeting his or her CHD risk at all and, if so, which intervention would be the most beneficial for this caregiver based on his or her stressors and resources.

Materials and Methods

Participants

The participants of this study were enrolled between 2/2015 and 1/2019 in the University of California, San Diego (UCSD) Dementia Caregiver Study for a randomized controlled trial aimed at improving caregiver psychobiological health through behavioral interventions (ClinicalTrials.gov registration number: NCT02317523). Here, we report the biomarker data, specifically the intervention effects on changes in the prespecified primary endpoint measure IL-6 from pre- to posttreatment. Prespecified secondary endpoints were changes in CRP, TNF-α, D-dimer, VWF, and PAI-1 from pre- to posttreatment.

Applying a community sampling strategy, we recruited caregivers through the UCSD Alzheimer's Disease Research Center, from local support groups, through referrals from local caregiver agencies and other participants, and from health fairs. To be eligible, caregivers had to provide at least 20 hours per week of in-home care for a spouse/partner with dementia, to be at least 55 years of age, and to perceive at least mild psychological distress, based on a score ≥5 on the Patient Health Questionnare-9 (27) at study enrollment. Exclusion criteria were current treatment with anticoagulants, nitrates, niacin, nonselective β-blockers, aldomet, labetalol or steroids; cognitive impairment, blood pressure >200/120 mm Hg; major psychiatric illnesses (eg, schizophrenia, bipolar disorder); a diagnosis of a terminal illness with a life expectancy < 1 year (in caregiver or care recipient); and caregiver receiving psychotherapy.

The Consort flow diagram showing the flow of participants through the stages of this biomarker study is displayed in Figure 1. We assessed 325 participants for eligibility, of which 151 met our inclusion criteria and were willing to undergo treatment by random. Some caregivers did not provide biomarkers at posttreatment and others elected to drop out or not do a posttreatment assessment. Thus, for this biomarker analysis, we examined data from 123 dementia caregivers who provided blood samples for biomarker assessment pre- and posttreatment. All participants provided written consent in the study protocol approved by the UCSD Institutional Review Board.

Interventions

Using a randomization table, eligible caregivers were randomly assigned in a 1:1 ratio to one of the two intervention groups. We previously described the intervention protocol in detail (24). Briefly, both interventions were conducted in caregivers' homes and consisted of six face-to-face therapy sessions of 60 minutes over a period of 12 weeks (ie, the interval between pre- and posttreatment assessments). The experimental intervention was behavioral activation (ie, PEP) to reduce activity restriction and restore engagement in pleasurable and

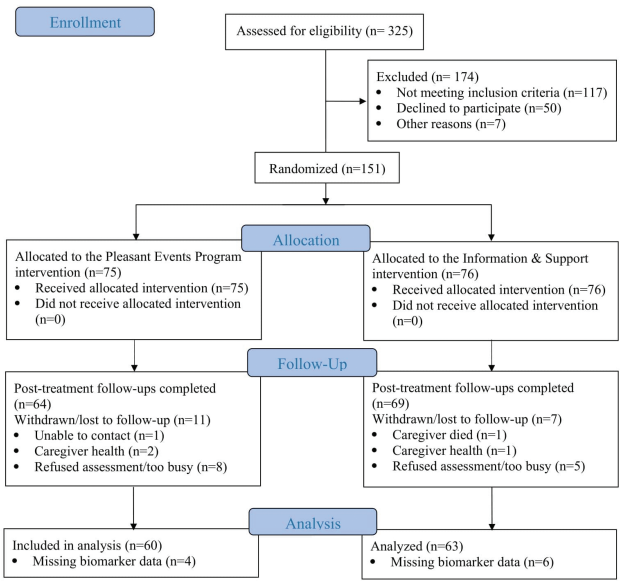

Figure 1. CONSORT flow diagram of participant allocation, follow-up and analysis. Full color version is available within the online issue.

rewarding activities through self-monitoring, while simultaneously reducing negative avoidant coping responses. Behavioral activation is an evidence-based treatment to alleviate psychological distress, including depression and negative affect (NA) in caregivers (23,24). The active comparator intervention was IS, which consisted of providing education on dementia, community-based services available for caregivers, and coping with caregiving specific stressors through problem-solving, supportive, and cognitive-behavioral therapy strategies. Caregivers receiving IS choose information relevant to their current circumstances to be discussed with their therapist.

Measures

The pretreatment baseline visit consisted of an interview-based assessment by a trained research associate in caregivers' home. The interview took approximately 1.5–2 hours and included administration of questionnaires, as well as questions about demographic factors and health characteristics. A research nurse collected fasting blood samples in caregivers' homes for biomarker assessments before and after treatment.

Demographics, Comorbidity, and Health Behaviors

Information on age and sex were collected and noted. Physical diseases were assessed by asking caregivers the question "Do you currently have, or has a doctor ever told you that you have any of the following health problems (heart attack, stroke, high blood pressure, heart disease, diabetes, high cholesterol, lung disease, liver disease, kidney problems, sleep apnea, cancer, thyroid disease)?" Affirmative responses were summed reflecting medical comorbidity (total score 0–12) (28). Smoking status was categorized into ever (ie, all former plus five current smokers) versus never smokers. The Rapid Assessment of Physical Activity (RAPA) scale was used to assess the amount of light, moderate and strenuous physical activities in a typical week; higher scores indicate greater amount of physical activity (total score 0–6) (29). The research associate measured weight and height to calculate the body mass index (BMI).

We formed a health behavior risk score (range 0–5) that was used for statistical analysis. Two risk points each were assigned to obesity (BMI ≥30 kg/m^2) and under-active regular light physical activity or sedentary; one risk point each was assigned to overweight (BMI ≥25 kg/m^2, but <30 kg/m^2), ever smoking, and under-active regular physical activity.

Indicators of Caregiving Stress

Information on years caregiving was obtained. Functional impairment of the care recipient was assessed with the Activities of Daily Living Questionnaire for patients with dementia covering areas referring to self-care, household, employment, shopping, travel, and communication (30). Total scores express percent impairment (0%–100%) in performing these activities. We categorized care recipients into two groups, those with severe (ie, 67%–100%) impairment and those with moderate (ie, 34%–66%) or none-to-mild (ie, 0%–33%) impairment, because the latter group comprised only six individuals. Twenty-four memory, disruptive, and depressive behaviors of the care recipient in the previous week and caregiver distress due to these behaviors were measured with the Revised Memory and Behavior Problem Checklist. Caregivers were asked to rate on a 5-point Likert scale how bothered or upset they felt by each behavior (0 = not at all, 4 = extremely; total score 0–96); higher scores indicate greater level of problem behavior distress which is expressed as the average item score (ie, total score divided by 24) (31). The 20-item Positive and Negative Affect Scale was applied to assess positive (eg, excited, active) and negative (eg, upset, afraid) affect in the past few weeks (total score 10–50 for each scale); higher scores indicate greater level of positive affect (PA) or NA (32). For regression analyses, we divided total PA and NA scores by 2.5, a clinically meaningful mean scale difference (32). The seven-item Pearlin Personal Mastery scale was used to rate feelings of having control over one's life circumstance (eg, "what happens to me in the future mostly depends on me"); higher scores indicate greater mastery (total score 7–28) (33).

Circulating Biomarkers

Blood samples were collected in EDTA tubes for IL-6, CRP, and TNF-α, and in sodium citrate tubes for D-dimer, PAI-1, and VWF and centrifuged for 15 minutes at 1,732 g force at 4°C. Plasma was stored at −80°C until analyzed in the USCD Integrative Health and Mind-Body Biomarker Laboratory. Concentrations of IL-6 and TNF-α were measured using an electrochemiluminescence-based multiarray sandwich immunoassay method through the MSD Human Proinflammatory Panel-1 V-PLEX 10-spot multiplex kit (Meso Scale Diagnostics LLC, Rockville, MD). Concentrations of CRP, PAI-1 antigen, D-dimer, and VWF antigen were determined with a quantitative sandwich enzyme immunoassay method (R&D Systems Human CRP and PAI-1 Quantikine ELISA kits, Biotechne, Minneapolis, MN; Thermo Scientific Human D-Dimer and VWF ELISA kits, Life Technologies, Carlsbad, CA). Intra- and interassay coefficients of variation were <10% for all analyses. Assay sensitivities were excellent.

Statistical Analysis

Data were analyzed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL) with level of significance at $p < .05$. A few missing values for physical diseases (seven cases), BMI, smoking status, care recipient functional impairment, caregiver problem behavior distress, personal mastery, and individual biomarkers pre- and posttreatment (all ≤3 cases) were replaced using the expectation maximization algorithm. Because of a non-Gaussian distribution, biomarker values were log (base 10) transformed prior to analysis. For clarity, we present original units.

Independent samples *t*-test and Pearson chi-square test were used to compare the PEP with the IS intervention group on characteristics assessed before treatment. Repeated-measures analysis of variance was used to test for differences in biomarker levels from pre- to posttreatment between the PEP and IS intervention group (ie, time-by-treatment interactions) with change in IL-6 levels as the primary outcome. Changes in CRP, TNF-α, D-dimer, PAI-1, and VWF levels were secondary outcomes. Main effects for time and treatment were of additional interest.

Binary endpoints facilitate individualized treatment decisions based on risk/benefit considerations (34,35). Therefore, we modeled logistic regression analysis with the binary dependent variable "decrease" (1 = yes, 0 = no) to estimate the relative chance that an indicator of caregiving stress would be associated with a decrease in biomarker levels from pre- to posttreatment, regardless the absolute value of this decrease. Accordingly, the regression output is organized such that odds ratios (OR) >1 indicate the relative chance of a reduction in biomarker levels (percentage value), with a one-unit increase in an independent variable, simultaneously adjusting for the others. The independent variables examined reflecting caregiver burden/distress were years caregiving, care recipient functional impairment, caregiver problem behavior distress, and NA. The examined resources of

caregivers were PA and personal mastery. Distressed dementia caregivers (36) and those utilizing effective coping skills (37) were shown to particularly benefit in terms of mental health outcomes in psychosocial interventions. Therefore, we hypothesized the chance of a beneficial biomarker response to treatment to be greater in caregivers with higher versus those with lower pretreatment levels of both burden/distress and resources.

In a supplementary linear regression analysis, we tested whether there would also be a continuous relationship between the above indicators of caregiving stress and the percentage change in absolute levels of biomarkers from pre- to posttreatment. Percentage changes were calculated on original values followed by log transformation. Log-transformed values deviating more than 3 *SD*s from the sample mean were omitted for analyses; so, sample sizes for the individual biomarker analyses range between $n = 119$ and $n = 122$.

In all regression models, six indicators of caregiving stress were explored as predictors of biomarker responses irrespective of the treatment condition (ie, main effects) and as moderators of the relative effect of each treatment condition on biomarker responses (ie, interaction effects). These indicators of caregiving stress were years caregiving, care recipient functional impairment, problem behavior distress, NA, PA, and personal mastery. Adjustment was made a priori for age, sex, the number of physical diseases, and the health behavior risk score as potentially confounding variables. Given our sample size, we allowed a maximum of 12 independent variables to prevent over-adjustment in regression models. Model outputs indicated no concern for multicollinearity.

Results

Characteristics of the Sample

Table 1 shows the characteristics of the 123 caregivers per treatment condition. Compared to caregivers randomized to the PEP condition ($n = 60$), those randomized to the IS condition ($n = 63$) were more frequently ever smokers; however, the health behavior risk score showed no group difference. There were also no significant group differences in terms of demographic factors, the number of comorbid physical diseases or indicators of caregiving stress.

Biomarker Levels and Intervention Effects

Table 2 shows biomarker levels at pre- and posttreatment for the entire sample and for each treatment condition separately. The results of the repeated measure analysis of variance are also shown. There were no significant time-by-treatment interactions for any biomarker, suggesting that the PEP condition had no effect on biomarkers. There were also no significant time effects, suggesting that biomarker levels did not change from pre- to posttreatment in the entire sample of caregivers regardless the treatment condition. The nonsignificant treatment effects additionally suggested that biomarker levels were similar in caregivers in the PEP group and those in the IS group both before treatment and at the end of treatment.

Relative Chance for a Reduction in Biomarkers from Pre- to Posttreatment

Indicators of caregiving stress as predictors of a biomarker reduction

Regardless of the randomization assignment, 56 caregivers showed a decrease and 67 showed an increase in IL-6 levels over the 12 weeks. The corresponding numbers were 63 and 60 for CRP, 55 and 68 for TNF-α, 66 and 57 for both D-dimer and PAI-1, and 64 and 59 for VWF. The logistic regressions of stressors and resources on a decrease in biomarker levels (yes vs no) from pre- to posttreatment, adjusted for demographic factors, the number of diseases and the health risk score, are summarized in Table 3. Whereas treatment was not a significant predictor, several indicators of caregiving stress predicted significantly and independently the chance for a reduction in IL-6, CRP, TNF-α, and D-dimer levels over the 12 weeks.

Most consistently, the higher the level of personal mastery, the more likely caregivers showed a reduction in all of these biomarkers. In detail, for a one-unit increase on the mastery scale before treatment, there was a 19% greater chance for a decrease in IL-6 levels from pre- to posttreatment ($p = .023$); the corresponding chances were 19% for CRP ($p = .026$), 28% for TNF-α ($p = .002$), and 21% for D-dimer ($p = .018$) levels. As opposed to caregivers whose spouse, at the most, had moderate levels of functional impairment before treatment, caregivers with a spouse with severe impairment in activities of daily living had a 4.8- and 2.6-fold greater chance for a reduction in CRP ($p < .001$) and D-dimer ($p = .036$) levels, respectively. In addition, caregivers with a one-unit increase in problem behavior distress prior to treatment, showed a 2.4- and 2.2-fold greater chance for a reduction in IL-6 ($p = .015$) and CRP ($p = .032$) levels, respectively. Caregivers with higher pretreatment NA to the extent

Table 1. Pretreatment Characteristics of 123 Study Participants by Treatment Condition

	Pleasant Events Program ($n = 60$)	Information Support ($n = 63$)	*p*
Age (years), mean (*SD*)	72.5 (7.6)	73.4 (7.5)	.513
Sex (female), *n* (%)	47 (78.3)	48 (77.2)	.777
Years caregiving, mean (*SD*)	5.33 (3.76)	4.40 (2.99)	.131
Physical diseases (*n*), mean (*SD*)	1.50 (1.19)	1.75 (1.31)	.277
Body mass index (kg/m^2), mean (*SD*)	26.6 (5.0)	28.1 (6.2)	.133
Ever smoking, *n* (%)	20 (33.3)	34 (54.0)	.021
Physical activity, mean (*SD*)	3.33 (1.70)	3.63 (1.56)	.307
Health behavior risk score, mean (*SD*)	2.25 (1.40)	2.40 (1.45)	.569
Severe functional impairment of CR, *n* (%)	36 (60.0)	27 (42.9)	.057
CR problem behaviors, mean (*SD*)	11.1 (4.1)	12.4 (4.1)	.094
CG problem behavior distress, mean (*SD*)	2.53 (0.63)	2.59 (0.58)	.629
Negative affect, mean (*SD*)	20.6 (7.3)	21.6 (6.2)	.424
Positive affect, mean (*SD*)	33.2 (7.3)	33.7 (6.9)	.689
Personal mastery, mean (*SD*)	12.0 (2.8)	12.7 (3.4)	.263

Note: CG = caregiver; CR = care recipient.

Table 2. Biomarker Levels Pre- and Posttreatment and Intervention Effects

Biomarker	Treatment Condition	Pretreatment	Posttreatment	*p*
IL-6 (pg/mL)	PEP + IS (*n* = 123)	0.67 (0.43–1.11)	0.68 (0.41–1.28)	
	PEP (*n* = 60)	0.68 (0.41–1.05)	0.67 (0.39–1.18)	
	IS (*n* = 63)	0.66 (0.50–1.26)	0.68 (0.49–1.53)	
	Time-by-treatment interaction			.854
	Time effect			.764
	Treatment effect			.165
CRP (mg/L)	PEP + IS (*n* = 123)	1.65 (0.64–3.43)	1.40 (0.71–3.20)	
	PEP (*n* = 60)	1.25 (0.57–3.08)	1.21 (0.55–2.78)	
	IS (*n* = 63)	1.73 (0.68–4.66)	1.53 (0.78–3.55)	
	Time-by-treatment interaction			.685
	Time effect			.813
	Treatment effect			.120
TNF-α (pg/mL)	PEP + IS (*n* = 123)	1.82 (1.54–2.43)	1.89 (1.57–2.41)	
	PEP (*n* = 60)	1.88 (1.55–2.42)	1.87 (1.47–2.48)	
	IS (*n* = 63)	1.78 (1.54–2.46)	1.91 (1.58–2.30)	
	Time-by-treatment interaction			.363
	Time effect			.434
	Treatment effect			.770
D-dimer (mg/L)	PEP + IS (*n* = 123)	5.09 (4.21–5.87)	4.90 (3.91-5,97)	
	PEP (*n* = 60)	4.79 (4.02–5.95)	4.75 (3.79–5.96)	
	IS (*n* = 63)	5.13 (4.30–5.85)	5.15 (4.28–6.12)	
	Time-by-treatment interaction			.530
	Time effect			.169
	Treatment effect			.302
PAI-1 (ng/mL)	PEP + IS (*n* = 123)	2.27 (1.31–3.83)	2.15 (1.23–3.80)	
	PEP (*n* = 60)	2.04 (1.18–3.82)	1.83 (1.09–3.57)	
	IS (*n* = 63)	2.44 (1.43–3.92)	2.37 (1.40–3.95)	
	Time-by-treatment interaction			.722
	Time effect			.244
	Treatment effect			.395
VWF (mg/L)	PEP + IS (*n* = 123)	13.5 (8.0–19.6)	13.3 (8.4–19.8)	
	PEP (*n* = 60)	14.8 (8.0–19.9)	15.3 (9.0–19.4)	
	IS (*n* = 63)	12.6 (7.0–18.2)	11.7 (7.7–20.6)	
	Time-by-treatment interaction			.421
	Time effect			.453
	Treatment effect			.383

Note: Values are median with interquartile range for the entire sample and each treatment condition separately. CRP = C-reactive protein; IL = interleukin; IS = information support; PAI = plasminogen activator inhibitor; PEP = pleasant events program; TNF = tumor necrosis factor; VWF = von Willebrand factor.

of a clinically meaningful mean scale difference had a 27% greater chance for a reduction in TNF-α levels (p = .008).

Indicators of caregiving stress as moderators of a biomarker reduction

To explore whether treatment condition was a moderator of the relation between indicators of caregiving stress and the chance for a decrease in biomarkers from pre- to posttreatment, we probed several interactions. There were significant interactions between treatment and care recipient functional impairment for IL-6 (p = .033), between treatment and NA for VWF (p = .020) and between treatment and PA for D-dimer (p = .043). Post hoc probing of these interactions revealed that severe care recipient functional impairment prior to treatment was associated with a greater chance for a reduction in IL-6 levels in caregivers in the IS group (OR = 3.045, 95% confidence interval [CI] 0.793, 11.696; p = .10) relative to those in the PEP group (OR = 0.602, 95% CI 0.157, 2.304; p = .46). Higher pretreatment NA was associated with a greater chance for a reduction in VWF levels in caregivers in the PEP group (OR = 1.185, 95% CI 0.911, 1.543; p = .21) relative to those in the IS group (OR = 0.797, 95% CI 0.615, 1.033, p = .086). Higher pretreatment PA was associated with a greater chance for a reduction in D-dimer levels in caregivers in the PEP group (OR = 1.008, 95% CI 0.804, 1.263; p = .95) relative to those in the IS group (OR = 0.548, 95% CI 0.383, 0.784; p < .001). There were no significant interactions between treatment and years caregiving, problem behavior distress, and personal mastery, respectively, for a change in any biomarker level.

Percentage Change in Biomarkers from Pre- to Posttreatment

The complementary linear regressions on (log) percentage change in biomarker levels from pre- to posttreatment, adjusted for demographic factors, the number of diseases and the health risk score, are summarized in Table 4. Treatment was not a significant predictor of the percentage change in any biomarker. Higher mastery before predicted a greater decrease in CRP (p = .022) and TNF-α (p = .025) levels. More severe care recipient functional impairment before treatment predicted a greater decrease in CRP levels (p < .001). Higher levels of pretreatment NA predicted a greater decrease in TNF-α levels (p = .015) and higher levels of pretreatment PA predicted a greater decrease in D-dimer (p = .028) levels. There was

Table 3. Logistic Regression Models for the Relative Chance for a Decrease in Biomarker Levels from Pre- to Posttreatment (n = 123)

Variables Entered	IL-6	CRP	TNF-α	D-dimer	PAI-1	VWF
Pleasant events program	0.903 (0.416, 1.961)	0.801 (0.358, 1.792)	1.494 (0.660, 3.379)	1.719 (0.768, 3.847)	1.057 (0.491, 2.272)	1.615 (0.763, 3.422)
Age	1.015 (0.962, 1.070)	1.033 (0.977, 1.092)	1.017 (0.962, 1.075)	1.010 (0.955, 1.067)	0.990 (0.940, 1.043)	1.008 (0.958, 1.061)
Female sex	0.905 (0.351, 2.331)	0.787 (0.299, 2.076)	0.461 (0.173, 1.225)	1.450 (0.541, 3.887)	0.651 (0.253, 1.676)	1.250 (0.505, 3.095)
Years caregiving	0.943 (0.832, 1.069)	0.917 (0.806, 1.044)	0.936 (0.822, 1.065)	0.921 (0.814, 1.042)	1.096 (0.968, 1.242)	1.027 (0.912, 1.155)
Physical diseases	0.995 (0.704, 1.405)	1.271 (0.881, 1.834)	0.733 (0.508, 1.058)	1.373 (0.929, 2.028)	0.999 (0.709, 1.406)	1.020 (0.728, 1.428)
Health behavior risk score	0.860 (0.631, 1.171)	0.903 (0.661, 1.235)	0.921 (0.672, 1.263)	0.998 (0.734, 1.357)	1.126 (0.832, 1.524)	0.878 (0.655, 1.176)
CR functional impairment	1.669 (0.708, 3.931)	4.804 (1.892, 12.194)***	1.302 (0.537, 3.155)	2.610 (1.065, 6.393)*	1.088 (0.474, 2.499)	1.314 (0.578, 2.984)
Problem behavior distress	2.441 (1.191, 5.000)*	2.244 (1.071, 4.702)*	0.853 (0.417, 1.749)	1.430 (0.691, 2.961)	0.688 (0.348, 1.361)	1.162 (0.600, 2.250)
Negative affect	0.953 (0.810, 1.120)	1.055 (0.894, 1.245)	1.272 (1.065, 1.520)**	1.608 (0.903, 1.263)	1.145 (0.971, 1.349)	1.006 (0.861, 1.175)
Positive affect	0.959 (0.825, 1.114)	1.038 (0.889, 1.212)	0.913 (0.782, 1.066)	0.816 (0.698, 0.954)*	1.063 (0.919, 1.229)	1.019 (0.885, 1.173)
Personal mastery	1.190 (1.025, 1.383)*	1.186 (1.020, 1.379)*	1.286 (1.095, 1.510)**	1.207 (1.033, 1.410)*	0.950 (0.825, 1.095)	1.060 (0.924, 1.216)

Note: Values are odds ratios (OR) with 95% confidence interval. An OR >1.0 indicates the relative chance of a reduction in the concentration of a circulating biomarker with a one-unit increase in a predictor variable. All predictors were entered in one block. Significance level: * $p < .05$, ** $p < .01$, *** $p < .001$.

CR = care recipient; CRP = C-reactive protein; IL = interleukin; PAI = plasminogen activator inhibitor; TNF = tumor necrosis factor; VWF = von Willebrand factor.

Table 4. Linear Regression Models for the Associations with (log) percentage Change in Biomarker Levels from Pre- to Posttreatment

Variables Entered	IL-6 (n = 121)	CRP (n = 119)	TNF-α (n = 119)	D-dimer (n = 121)	PAI-1 (n = 122)	VWF (n = 121)
Pleasant events program	0.032 (−0.070, 0.135)	−0.013 (−0.128, 0.103)	−0.045 (−0.118, 0.029)	−0.018 (−0.060, 0.024)	−0.047 (−0.155, 0.061)	−0.043 (−0.144, 0.059)
Age	−0.001 (−0.009, 0.006)	−0.005 (−0.013, 0.003)	−0.001 (−0.006, 0.004)	0.001 (−0.002, 0.004)	0.002 (−0.005, 0.010)	−0.007 (−0.014, 0.000)
Female sex	0.004 (−0.119, 0.128)	−0.075 (−0.214, 0.065)	0.049 (−0.039, 0.137)	−0.001 (−0.052, 0.050)	0.030 (−0.103, 0.163)	−0.114 (−0.236, 0.009)
Years caregiving	−0.001 (−0.017, 0.014)	0.017 (−0.001, 0.035)	0.006 (−0.005, 0.018)	0.006 (−0.001, 0.012)	0.001 (−0.016, 0.017)	−0.001 (−0.017, 0.015)
Physical diseases	−0.001 (−0.046, 0.045)	−0.013 (−0.065, 0.039)	0.022 (−0.011, 0.054)	−0.011 (−0.030, 0.008)	−0.013 (−0.061, 0.036)	0.020 (−0.025, 0.065)
Health behavior risk score	0.016 (−0.024, 0.055)	0.020 (−0.025, 0.064)	0.006 (−0.022, 0.035)	0.003 (−0.013, 0.020)	−0.011 (−0.054, 0.031)	−0.026 (−0.065, 0.014)
CR functional impairment	−0.028 (−0.140, 0.085)	−0.258 (−0.385, −0.131)***	−0.029 (−0.110, 0.051)	−0.044 (−0.090, 0.002)	−0.023 (−0.142, 0.096)	0.049 (−0.062, 0.161)
Problem behavior distress	−0.032 (−0.121, 0.057)	−0.078 (−0.179, 0.023)	−0.027 (−0.091, 0.037)	−0.033 (−0.070, 0.004)	0.001 (−0.093, 0.096)	0.045 (−0.044, 0.134)
Negative affect	0.001 (−0.020, 0.022)	−0.020 (−0.044, 0.003)	−0.019 (−0.034, −0.004)*	0.000 (−0.009, 0.008)	−0.020 (−0.042, 0.003)	0.007 (−0.014, 0.028)
Positive affect	0.000 (−0.019, 0.020)	0.000 (−0.023, 0.022)	−0.006 (−0.020, 0.007)	0.009 (0.001, 0.017)*	−0.016 (−0.036, 0.004)	0.002 (−0.017, 0.021)
Personal mastery	−0.019 (−0.037, 0.000	−0.025 (−0.046, −0.004)*	−0.015 (−0.029, −0.002)*	−0.006 (−0.014, 0.001)	0.001 (−0.019, 0.021)	0.003 (−0.015, 0.021)

Note: Values are unstandardized coefficients B with 95% confidence interval. Significance level: * $p < .05$, ** $p < .01$. CR = care recipient; CRP = C-reactive protein; IL = interleukin; NF = tumor necrosis factor; PAI = plasminogen activator inhibitor; VWF = von Willebrand factor.

also a significant interaction between treatment and care recipient functional impairment for VWF ($p < .05$). Post hoc probing showed an association between more severe care recipient functional impairment prior to treatment and a greater decrease in VWF levels in caregivers in the PEP group ($B = –0.029$, 95% CI: –0.199, 0.142; $p = .74$) relative to those in the IS group ($B = 0.121$, 95% CI: –0.049, 0.292; $p = .16$). There were no significant interactions between treatment and years caregiving, problem behavior distress, NA, PA, and personal mastery, respectively, for a change in any biomarker level.

Discussion

Principal Finding of Intervention Effects on Circulating Biomarkers

In this randomized controlled trial with 123 family dementia caregivers, we found no statistically significant decrease in circulating cardiovascular biomarkers with PEP, a brief behavioral activation intervention, compared to time-equivalent IS, an active control intervention. We further found that after 12 weeks of treatment, plasma levels of IL-6, our primary outcome measure, and of CRP, TNF-α, D-dimer, VWF, and PAI-1, our secondary outcome measures, were the same as before treatment. Therefore, neither intervention had any significant effect on biomarker levels over time across all caregivers. This result was robust, as there was also no significant main effect for treatment on biomarker outcomes in the fully adjusted regression analyses taking into account demographic factors, medical comorbidity, health behaviors and caregiver stressors and resources. Thus, we infer that by participating in either PEP or IS for 12 weeks, the *average* caregiver, even when showing mild level of psychological distress, cannot expect to improve in his or her cardiovascular biomarker profile.

The findings of the current trial partially contrast with those of our previous one in which we found a significant decrease in IL-6 with PEP compared to IS after 6 weeks of treatment (24). Differences in the study design might account for this discrepancy, including the different treatment duration, varying therapist characteristics and that mild psychological distress was an inclusion criterion only in the current trial. Consistently, neither trial showed a difference in D-dimer levels between the two treatment conditions. Clearly, before a definite verdict can be made as to whether psychosocial interventions are able to improve a biomarker-based cardiovascular risk profile in dementia caregivers, further randomized controlled trials are needed. Different interventions could also be tested (17,23), some of which have shown, for instance, potential to lower blood pressure (38,39), another important cardiovascular risk factor that is highly prevalent in dementia caregivers (40).

Secondary Exploratory Findings

Intriguing observations flow from our secondary observations. About half of the caregivers showed a decrease and the other half an increase in their biomarker levels over the 12-week study, explaining why on average the change in biomarkers in our sample was null. Furthermore, despite the fact that we found no simple effects of psychosocial interventions on biomarkers, we found that several indicators of caregiver burden/distress and resources were significantly predictive for a decrease in biomarker levels across all caregivers. To a lesser extent, indicators of caregiving stress were also significant moderators of the relative effect of PEP or IS on reductions in biomarkers. However, as our trial lacked a wait-list control condition, there is a possibility that the observed biomarker reductions, proposed as a function of stressors and resources, could reflect time instead of treatment effects. Furthermore, when interpreting these results, one must consider that they are based on a number of exploratory analyses, which may lead to spurious findings.

With these limitations in mind, either PEP or IS could be offered to caregivers whose spouse has severe functional impairment, or who have high levels of problem behavior distress, both NA and PA, or mastery in an attempt to lower biomarker levels. Most obviously, those with higher personal mastery, an important coping strategy and resilience factor associated with positive physical outcomes in dementia caregivers (41), were more likely to show a decrease in IL-6, CRP, TNF-α, and D-dimer levels altogether. Similarly, intervention trials have shown a greater benefit regarding mental health outcomes in dementia caregivers with high distress (32) and good coping skills (33). In turn, if a caregiver does not endorse sufficient stress or resources, cardiovascular harm might even increase with both these interventions. The latter perhaps because both situations could inflict stress, being treated when not feeling distressed or having to realize that resources are too low to translate the skills taught to everyday life.

Regarding moderator effects, we found some indication that caregivers in the PEP group were more likely to benefit in terms of a decrease in VWF and D-dimer when they had high level of NA and PA, respectively. One explanation could be that PEP was originally designed to target depressive symptoms (23), and PEP also improved NA in our previous clinical trial when compared with IS after six weeks (24). In turn, caregivers in the IS group were more likely to show a reduction in IL-6 when their spouse had severe functional impairment, maybe because in this scenario pragmatic aids to manage everyday life as a caregiver becomes all the more important. Effects might vary between biomarkers, as caregivers with a spouse with severe functional impairment prior to treatment had greater reduction in VWF when being in the PEP as opposed to the IS group. Of the biomarkers we assessed, VWF is arguably the most responsive to sympathetic activation (42), and it could be that PEP lowered VWF through a dampening of sympathetic nerve outflow in these caregivers. However, the present study was not designed to investigate biobehavioral mechanisms explaining main and moderating effects of stressors and resources on biomarker outcomes. The mechanisms presumably involved will have to be examined elsewhere, including improvements in both autonomic nervous system and hypothalamic-pituitary adrenal axis function, perceived distress, and coping skills (17,23).

Although fewer in number than in the logistic regression analysis, similar significant and independent associations between indicators of caregiving stress and percentage changes in biomarker levels emerged in a supplementary linear regression analysis. For instance, greater mastery was significantly predictive for the chance of a decrease in IL-6, but not for its magnitude. However, a clinician would primarily like to know whether an individual caregiver would show a reduction in biomarkers or not, but not so much to what extent. This is much like when a decision has to be made if, for instance, antihypertensive medication should be started in a patient with high blood pressure.

Potential Clinical Relevance

Although the role of biomarkers investigated for coronary sclerosis and thrombosis has been established (9–16,43,44), offering new targets for cardiovascular therapy (45), the clinical relevance of increased inflammation in family caregivers is a matter of debate (17,18). Bearing the exploratory nature of our analyses in mind, our study suggests that with appropriate treatment some family dementia caregivers' physical health could indeed benefit from lowering inflammation, as well as coagulation biomarkers, like IL-6, CRP, TNF-α, and D-dimer. Further studies are worth pursuing this hypothesis. Also, whereas the full sequence of stressors and resources to inflammation

(46) and coagulation (42) to CHD remains to be established, our findings might reach beyond implications for caregiver cardiovascular health. This is exemplified for IL-6, a cytokine that shows robust responses to psychosocial stress (47). The IL-6 signaling axis is involved in numerous chronic inflammatory diseases (48), and circulating IL-6 shows associations with numerous metabolites in older adults (49). Accordingly, high IL-6 levels have for instance been associated with frailty (50), longitudinal changes in brain function in older adults (51), and perceived physical fatigability in men and women aged 50–96 years (52). In agreement with this literature, a recent study showed that high IL-6 levels were predictive of emergency department visits in dementia caregivers during a follow-up of 15 months (53).

Limitations

We did not achieve to enroll the target sample size of 200 participants; so, limited statistical power is an issue. The analyses on predictors and treatment moderators of biomarker outcomes were secondary, did not adjust for multiple comparison, and thus are to be understood as hypothesis testing justified by the fact that research like this is still rare. Since only four of the numerous interactions tested between treatment and six different indicators of caregiving stress were statistically significant, these effects could be spurious and should be interpreted with caution. At least some of the effects of predictors on changes in biomarkers could be explained by regression to the mean because no adjustments were made for pretreatment levels of biomarkers; technically, this is not possible for measures of a dichotomous change (any increase vs any decrease in a particular biomarker). We reported on biomarker data assessed before and after treatment, while the 2-year follow-up data are still being collected and analyzed. Our findings may not translate to caregivers of a spouse without dementia, to significantly younger caregivers taking care of a parent with dementia, and to caregivers providing end of life care (54). Consistent with the healthy caregiver hypothesis (55), medical comorbidity was rather low in our sample for this age. Due to the sample size, we were not able to adjust for factors that could have influenced biomarker levels additionally, such as medications, so residual confounding remains possible.

Conclusions

The PEP is unlikely a more effective treatment than IS in lowering biomarkers of increased CHD risk in family dementia caregivers after 12 weeks. However, family dementia caregivers who show both high levels of stressors and resources prior to treatment could benefit from psychosocial interventions in terms of an improved cardiovascular risk profile. This knowledge is novel, although based on exploratory analyses, and thus should be confirmed in further studies before personalized treatment recommendations can be made for dementia caregivers.

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Conflict of Interest

None reported.

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