

Factors associated with the risk of cardiovascular disease in family caregivers of people with dementia: a systematic review

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Abstract

Objective: This study aimed to systematically review studies that reported factors associated with the risk of cardiovascular disease (CVD) in family caregivers of people with dementia (PWD).

Methods: Literature was searched in PubMed, Medline, CINAHL, and PsycINFO using keywords generated from the terms “dementia”, “caregiver”, and “cardiovascular disease”. We included studies that examined factors associated with CVD risk in family caregivers of PWD, those with longitudinal or cross-sectional study designs, and those published in English.

Results: A total of 34 studies were included in this review. Stress and depressive symptoms, pleasant leisure activity, coping self-efficacy and coping strategy, physical activity, and social support were the main modifiable associated factors of CVD risk in family caregivers of PWD. However, the association between sleep and CVD risk was unclear. Caregiving status, the duration of caregiving, genes, and race, were the main non-modifiable associated factors of CVD risk in family caregivers.

Conclusion: This review showed seven modifiable factors of CVD risk. In particular, leisure activities, physical activity, and social support were significantly negatively associated with the risk of CVD. Researchers and clinical professionals are recommended to consider these risk factors when they develop interventions to reduce CVD risk in family caregivers of PWD.

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Keywords

Dementia, caregiver, cardiovascular disease, blood pressure, systematic review, social support, leisure activity, risk factor

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Background

Dementia is one of the major causes of disability and dependency in older people; and it is currently the seventh leading cause of death worldwide.¹ Most people with dementia (PWD) receive care at home from family caregivers² who are responsible for most daily activities, including feeding, bathing, assisting with toileting, and dressing.³ The term “family caregivers” refers to non-professional people who provide unpaid care for others at home. Family caregivers have a major challenge in taking care of their relatives with dementia because the behavioral and psychological symptoms of dementia are difficult to deal with.⁴

Family caregivers of PWD are usually considered to be “invisible second patients”. Caregiving tasks have a negative effect on family caregivers’ physical health.⁵ Two meta-analyses reported that informal caregivers suffered poorer physical health conditions than did non-caregivers.^{5,6} Furthermore, caregivers had lower scores on a self-reported general health questionnaire and the Health-Related Quality of Life questionnaire than did non-caregivers.⁷ Family caregivers of PWD also engage in fewer physical activities, experience more sleep disturbance, and have a higher risk of malnutrition than do non-caregivers.^{8–10}

There is a growing body of research that has focused on impairment of cardiovascular health of caregivers.^{11–14} Cardiovascular disease (CVD) is the leading cause of death worldwide, and approximately 17 million

people die from CVD each year.¹⁵ Recent studies have reported that caregivers have a higher risk of developing CVD than do non-caregivers.¹⁶ Long-term exposure to chronic stress may also produce changes in the emotional and physiological responses that affect susceptibility to disease, especially CVD.¹⁷ Caregivers of PWD experience a higher level of stress and depressive symptoms compared with caregivers of loved ones with other chronic diseases and disabilities.^{18,19}

Family caregivers of PWD show a higher risk of suffering from hypertension than do non-caregivers.^{20–22} Hypertension is the main risk factor for CVD.²³ Caregivers also have higher pro-coagulant molecule D-dimer (DD)²⁴ and pro-inflammatory cytokine interleukin (IL)-6²⁵ concentrations relative to non-caregivers, which may result in a pro-thrombotic and pro-inflammatory status. Elevations in serum levels of IL-6, DD, and C-reactive protein (CRP) are associated with higher risks of cardiovascular disorders, autoimmune diseases, frailty, and mortality.^{26,27}

Family caregivers of PWD who suffer from CVD experience a higher risk of morbidity and mortality,¹⁵ which in turn decreases their ability to take effective care of their relatives. Understanding the risk factors of CVD in family caregivers of PWD before implementing interventions is important. However, there have been no systematic reviews that examined factors associated with CVD in family caregivers of PWD. Therefore, this study aimed to

systematically review studies that reported associated factors of CVD risk to determine the factors of CVD in family caregivers of PWD.

Methods

Search strategy

Articles were identified from four electronic databases, including PubMed, CINAHL, Medline, and PsycInfo, published from 31 December 1987 to 31 December 2017. The key search terms were generated from the terms “dementia”, “caregiver”, and “cardiovascular disease”. The search keywords were (dementia OR Alzheimer OR “cognitive disorder”) AND (caregiver* OR carer OR “caring personnel”) AND (“cardiovascular diseases” OR “myocardial ischemia” OR “coronary artery disease” OR infarct* OR ischemic OR heart diseases OR hypertension OR “blood pressure”). The search process was conducted between November 2017 and December 2017. During the search process, the authors first browsed the title and the abstract of each article. If the title and the abstract were related to the review topic (with an overall agreement found to be 90%), the full text was extracted to research the details of each study. Each study was retrieved according to the PRISMA guidelines (<http://www.prisma-statement.org/>).

Inclusion and exclusion criteria

This review included primary studies that examined the risk factors of CVD among family caregivers of PWD. Those studies were designed as longitudinal or cross-sectional studies and were published in English. The factors associated with the risk of CVD were found in cross-sectional studies, and the causal relationship between caregiving situation-related factors and

CVD risks were determined from longitudinal studies.

The exclusion criteria were studies that did not primarily focus on the risk factors associated with CVD in family caregivers of PWD, and studies that were published in a language other than English. Systematic reviews, editorials, letters to the editor, theses, and practice guidelines were excluded from this review. Interventional or experimental studies were also excluded because the outcomes were likely to be changed after the intervention.

Data extraction and synthesis

The authors reviewed the titles, abstracts, and the content of the selected articles. One reviewer extracted data from each study while the other read each article to check the accuracy and completeness of the extracted data. The study type, population, number of participants, age, factors associated with the risk of CVD, measurements of study outcomes, and results were extracted from the selected papers and incorporated in an evidence table according to Cochrane’s guidelines.²⁸

Quality appraisal

The study quality was evaluated by a standardized critical appraisal instrument from the Study Quality Assessment Tools offered by the National Institutes of Health of the United States.²⁹ Two reviewers assessed the quality of the reviewed studies separately under this standardized critical appraisal instrument. Discrepancies were solved by a third researcher. The criteria of the National Institutes of Health²⁹ were used to assess the quality of the studies. Each study was assigned an overall quality rating of good, fair, and poor according to the above-mentioned criteria. This overall rating was determined by the number of criteria that the study met and the risk for

potential bias. One cross-sectional study³⁰ and one longitudinal study³¹ were rated as fair because of their small sample sizes ($n < 40$).

Results

Search outcome

Figure 1 shows the results of the search (PRISMA flow chart). A total of 756 records were identified from four databases. Of those, 236 duplicate studies were excluded, as well as another 473 irrelevant studies after screening titles and abstracts. After reviewing 47 full texts, 13 studies were excluded. The excluded studies included six theses, one book section, four

randomized, controlled trials, one study in which the population did not comprise family caregivers of PWD, and one study that did not examine the associated factors of CVD risk. Finally, 34 studies were included in this systematic review. Among the selected studies, 25 of them were cross-sectional studies.

A total of 4638 participants were included in this review, including 3689 family caregivers of PWD and the other participants were non-caregiving controls. Most of the family caregivers were older (age ≥ 55 years), spousal caregivers ($>55\%$), and women (75%). Nearly 90% of the participants were from the United States. Table 1 shows the table of evidence of the reviewed studies.

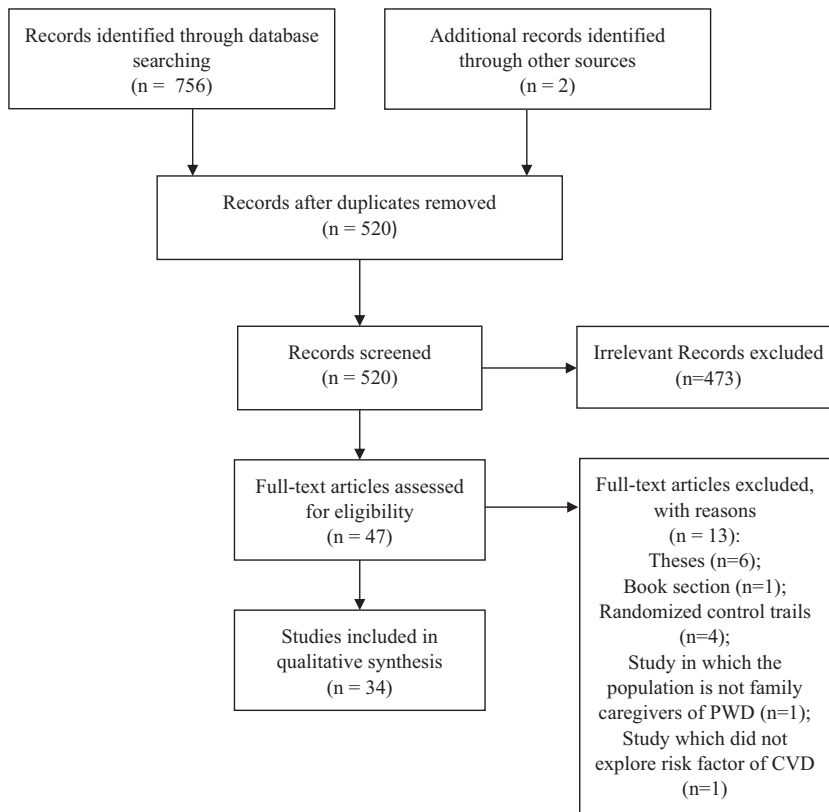


Figure 1. PRISMA flow diagram of the study.

Table 1. Characteristics of the reviewed studies.

Author (year)	Population	Number of participants	Age (years)	Factors associated with CVD risk	Outcome measures	Results	Study quality
Wu et al., 2017*	USA	146: 96 spouse caregivers, 50 non-caregiving controls	≥ 55	Years of caregiving: long-term caregivers (providing care ≥4 years); short-term caregivers (providing care <4 years)	SBP and HR were used to assess cBRS by LabVIEW software	Long-term caregiving: †cBRS (0.860 ± 0.033; p = 0.013) Short-term caregiving: ‡cBRS (0.911 ± 0.028; p = 0.144)	Good
Mausbach et al., 2017#	USA	126	74.2 ± 7.9	Engagement in pleasant leisure activities	BP	ΔPleasant leisure activities with MAP (B = -0.08, SE = 0.04, p = 0.040) and DBP (B = -0.07, t = -2.18, p = 0.030)	Good
Márquez-González et al., 2017*	NA	79	58.4 ± 13.56	Experiential avoidance	BP	†Avoidant behaviors and intolerance of negativity factors and BP	Good
Laks et al., 2016*	Brazil	209	42.1	Caregiving	Self-reported hypertension	†Caregiving and hypertension (OR, 1.584; p < 0.015)	Good
Ho et al., 2014*	USA	84	70.7 ± 8.4	Years of caregiving: AR	Resting plasma NE and EPI levels	High AR: †Years of caregiving and EPI Low AR: ‡Years of caregiving and EPI	Good
Schwartz et al., 2013*	USA	126	74	Sleep	Hypertension was defined either by self-reporting and current use of a prescribed antihypertensive, or as resting SBP or SBP of 90 or 140 mmHg, respectively	‡Nighttime sleep duration, percentage of sleep at night, and daytime naps with hypertension (OR, 0.97; 95% CI, 0.62–1.52; OR, 1.02; 95% CI, 0.93–1.11; OR, 1.10; 95% CI, 0.44–2.74, respectively)	Good
Hoshino et al., 2013*	Japan	304: 150 female caregivers and 154 female non-caregiving controls	Caregivers: 62.4 ± 12.2; controls: 62.7 ± 2.1	Menopause; carbohydrate energy ratio; 24-h Na excretion in urine	Hypertension was defined by current use of an antihypertensive prescription; BP	†Caregiving and hypertension (p < 0.05) ‡Having menopause hypertension (OR, 23.93; 95% CI, 2.75–208.32)	Good

(continued)

Table 1. Continued.

Author (year)	Population	Number of participants	Age (years)	Factors associated with CVD risk	Outcome measures	Results	Study quality
Chatillon et al., 2013*	USA	66	55	High engagement in pleasant events plus low perceived activity restriction (HPLR); low pleasure plus high restriction (LPHR); high pleasure plus high restriction or low pleasure plus low restriction (HPLR/LPLR)	BP	Participants with HPLR (86.78 mmHg) had significantly lower MAP compared with those with LPHR (94.70 mmHg) ($p = 0.01$, Cohen's $d = 0.89$) and those with HPLR/LPLR (94.84 mmHg) ($p = 0.023$, Cohen's $d = 0.91$)	Good
Roepke et al., 2012*	USA	110	74 ± 8	Duration of care	IMT	†Duration of care and IMT ($\beta = 0.202$, $p = 0.044$)	Good
Gouin et al., 2012*	USA	130: 53 caregivers and 77 non-caregiving controls	Caregivers: 64.3 ± 11.17; controls: 65.97 ± 14.35	Caregiving; daily stressor	IL-6 and CRP	†Caregiving and CRP levels ($\beta = 0.19$, $t(128) = 2.23$, $p = 0.03$, $R^2 = 0.037$) †Daily stressors with IL-6 levels ($\beta = 0.05$, $t(109) = 2.06$, $p = 0.04$, $R^2 = 0.034$) and CRP ($\beta = 0.9$, $t(129) = 2.14$, $p = 0.04$, $R^2 = 0.036$)	Good
Von Känel et al., 2011*	USA	169: 115 Alzheimer's caregivers and 54 non-caregiving controls	Caregivers: 73.8 ± 8.2; controls: 74.4 ± 6.3	Caregiving; physical activity	Cardiometabolic risk factors were defined by a clinical diagnosis of MetS using guidelines suggested by the Adult Treatment Panel III	†Low levels of physical activity: Caregiving and cardiometabolic risk score (0.58 ± 0.31 vs. -1.23 ± 0.54 , $p = 0.017$) ‡High levels of physical activity: Caregiving and cardiometabolic risk score ($p = 0.81$)	Good
Von Känel et al., 2011#	USA	174: 119 spousal caregivers and 55 non-caregiving controls	75 ± 8	Caregiving; placement and death of spouses; depressive symptoms; sleeping difficulties	MetS factors related to adiposity, dyslipidemia, hypertension, and hyperglycemia	†Caregiving and MetS factors (1.78 ± 0.13 vs. 1.36 ± 0.18 , $p = 0.008$) ΔDeath of the spouse with SBP (-6.2 ± 2.6 mmHg, $p = 0.019$) and DBP (-3.4 ± 1.5 mmHg, $p = 0.026$) ΔLower levels of depressive symptoms and sleeping difficulties Placement of the spouse and MetS factors	Good

(continued)

Table 1. Continued.

Author (year)	Population	Number of participants	Age (years)	Factors associated with CVD risk	Outcome measures	Results	Study quality
Mausbach et al., 2011*	USA	62	74	Stress; self-efficacy	IL-6	†Low self-efficacy, stress and IL-6 ($\beta = 0.43$) ‡High self-efficacy: stress and IL-6 ($\beta = -0.10$)	Good
Harmell et al., 2011*	USA	100	73.8 ± 8.14	Self-efficacy	BP	ΔSelf-efficacy for problem-focused coping and MAP, SBP, and PP	Good
Kring et al., 2010*	USA	248: 126 White caregivers and 122 White non-caregiving controls	Caregivers: 63.2 ± 13.1; controls: 60.0 ± 14.4	TT genotype	Serum HDL cholesterol (mg/dL) and serum triglycerides (mg/dL)	ΔTT genotype with waist circumference (interaction, $p = 0.026$), triglyceride levels (interaction, $p = 0.001$), and high-density lipoprotein cholesterol levels (interaction, $p = 0.001$)	Good
Von Känel et al., 2008*	USA	105: 64 caregivers and 41 non-caregiving controls.	70 ± 8	Caregiving	Framingham CHD risk score	†Caregiving CHD risk score (8.0 ± 2.9 vs. 6.3 ± 3.0 points, $p = 0.013$)	Good
Mausbach et al., 2007#	USA	165: 112 caregivers and 53 non-caregiving controls	Caregivers: 72.8 ± 8.7; controls: 67.4 ± 6.9	Caregiving	t-PA antigen	ΔCaregiving t-PA antigen	Good
Mausbach et al., 2007#	USA	643	57	Depressive symptoms; distress	Self-reported cardiovascular disease and hypertension	†Depressive symptoms ($p = 0.040$) and distress from patients' problem behaviors ($p = 0.034$) with CVD diagnosis	Good
Knight et al., 2007*	USA	204: 102 caregivers and 102 non-caregiving controls	≥55	Race	Cardiovascular measures were BP and HR	†African Americans and SBP ($F(1, 184) = 6.74$, $p = 0.01$, $MSE = 541.75$)	Good

(continued)

Table 1. Continued.

Author (year)	Population	Number of participants	Age (years)	Factors associated with CVD risk	Outcome measures	Results	Study quality
Kim et al., 2007*	USA	160: 95 African Americans and 65 White individuals	White: 56.62 ± 16.35; African Americans: 54.71 ± 15.27	Race; coping	HR and BP	ΔAfrican Americans with SBP ($p < 0.001$) and DBP ($p < 0.001$) †Active coping and DBP ($p < 0.01$)	Good
Mausbach et al., 2006*	USA	40	73 ± 8	Sleep	Plasma DD and NE	†Awake after sleep onset with NE levels ($\beta = 0.35$; $t = 2.45$, $df = 32$, $p = 0.020$) and plasma DD levels ($\beta = 0.31$; $t = 2.18$, $df = 29$, $p = 0.038$)	Good
Wilcox et al., 2005*	Columbia, South Carolina area	28: 16 Caucasians and 12 African Americans	64 ± 10	Race	BP, HR, salivary cortisol	†African American women with SBP, DBP, and HR	Fair
Von Känel et al., 2005#	USA	68: 48 caregivers and 20 non-caregiving controls	72 ± 9	Caregiving	TAT, DD, vWF antigen, t-PA antigen, and PAI-1 antigen	†Caregiving and a marker of fibrin formation and degradation (688 ± 575 vs. 406 ± 157 ng/ml, $p = 0.021$) †Speech stress with HR ($p = 0.017$), SBP ($p = 0.002$), and DBP ($p < 0.001$)	Good
Von Känel et al., 2003#	USA	37	72 ± 6	Stress; negative life events	HR and BP	†The number of negative life-events and allostatic load ($R^2 = 0.125$, $F(1, 33) = 7.49$, $p = 0.010$) †The number of negative life events and plasma DD levels ($p = 0.010$)	Fair
Von Känel et al., 2003*	USA	54	73 ± 6	Stress; negative life events	TAT, DD, and vWF antigen	†Body mass index and life stress with DD levels	Good
Shaw et al., 2003#	USA	111	71.6 ± 6.5	Spousal problem behaviors; emotionally expressive; hostility	BP	†Spousal problem behaviors and being less emotionally expressive with DBP ($p < 0.05$) †More spousal ADL assistance and DBP ($p < 0.05$)	Good
Kiecolt-Glaser et al., 2003#	USA	225: 119 female caregivers and 106 non-caregiving controls	70.58 ± 8.03	Caregiving	IL-6	Caregivers' average rate of increase in IL-6 levels was approximately four times greater than that of non-caregivers	Good

(continued)

Table 1. Continued.

Author (year)	Population	Number of participants	Age (years)	Factors associated with CVD risk	Outcome measures	Results	Study quality
Von Känel et al., 2001*	USA	53	73	Stressor	HR, BP, TAT, DD, and vWF	†Stressor and DD levels ($p = 0.046$)	Good
Atienza et al., 2001*	Northern California	50: 25 men and 25 women caregivers	Men: 72.8 ± 9.6 ; women: 70.4 ± 8.1	Sex	BP and HR	†Female caregivers and SBP and DBP ($p \leq 0.01$)	Good
Shaw et al., 1999# ⁴	USA	191: 144 caregivers and 47 non-caregiving controls	Caregivers: 70.5 ± 7.0 ; controls: 70.2 ± 6.4	Patient problem behaviors; caregiver distress	BP	†Caregiving and hypertension ($p < 0.05$)	Good
Knight and McCallum, 1998*	USA	154: 110 White caregivers and 44 African American caregivers	White: 62.9 ± 12.6 ; African Americans: 57.7 ± 14.3	Race	HR and BP	Whites and African Americans showed significant HR reactivity in response to mental arithmetic and to relating to a caregiving story	Good
Uchino et al., 1994#	USA	31: 13 men and 18 women	61.87	Caregiver-patient pre-illness relationship	Cardiovascular reactivity	Caregivers' construals of pre-illness relationship with patients with Alzheimer's disease were differentially related to cardiovascular functioning	Good
Vitaliano et al., 1993*	USA	160: 82 caregivers and 78 non-caregiving controls	Caregivers: 69.4 ± 8.5 ; controls: 68.5 ± 5.9	Hostility; expressed emotion; avoidance coping	BP and HR	‡Higher hostility levels ($p < 0.001$), higher expressed emotion (criticism) ($p < 0.001$), and greater avoidance in response to emotional tasks ($p < 0.001$) with BP and SBP	Good
Uchino et al., 1992*	USA	60: 36 caregivers and 34 non-caregiving controls	63.5	Social support	BP and HR	†High levels of social support: age and SBP ‡Low levels of social support: age and SBP	Good

*Cross-sectional study; #longitudinal study; †significantly positively related to; ‡not significantly positively related to; Δsignificantly negatively related to
 ADL: activities of daily living; AR: activity restriction; BP: blood pressure; cBRS: cardiovascular baroreflex sensitivity; CHD: coronary heart disease; CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease; DD: D-dimer; DBP: diastolic blood pressure; EPI: epinephrine; HDL: high-density lipoprotein; HR: heart rate; IL-6: interleukin-6; IMT: intima-media thickness; MAP: mean arterial pressure; MetS: metabolic syndrome; MSE: mean square error; NA: not available; NE: norepinephrine; OR: odds ratio; PAI-1: plasminogen activator inhibitor 1; PP: pulse pressure; SBP: systolic blood pressure; TAT: thrombin-antithrombin III complex; t-PA: tissue-type plasminogen activator assay; vWF: von Willebrand factor.

Table 2. Common risk factors of CVD in family caregivers of PWD and in non-caregivers.

Common risk factors of CVD in non-caregivers	Common risk factors of CVD in family caregivers of PWD
Raised or altered blood cholesterol levels ⁸⁷	Caregiving status ³⁷
Raised triglyceride levels with low HDL-cholesterol levels ⁸⁸	Duration of caregiving ¹⁴
Diabetes ⁸⁹	Stress and depression ³⁶
High blood pressure ⁹⁰	Activity restriction ³⁹
Stress and depression ⁹¹	Low level of self-efficacy ⁵¹
Smoking ⁹²	Physical inactivity ³⁵
Excessive alcohol ⁹²	Avoidance in coping ⁵¹
Physical inactivity ⁹³	Lack of social support ¹²
Being overweight/obesity ⁹³	

CVD: cardiovascular disease; HDL: high-density lipoprotein; PWD: people with dementia.

Indicators for assessing CVD risk

Most studies showed that blood pressure (BP) and heart rate (HR) were factors that reflected cardiovascular status, and these were measured by noninvasive BP monitors following a standard procedure. To avoid diurnal effects of the participants, most of the BP measurements were taken in the morning. Some studies defined hypertensive status by participants' self-reports and current use of an antihypertensive prescription.³²⁻³⁴ Metabolic syndrome (Mets) factors, which include adiposity, dyslipidemia, hypertension, and hyperglycemia, were also used to reflect cardiovascular status.^{35,36} One study adopted the Framingham coronary heart disease risk score, which includes age, sex, smoker, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic BP, and BP being treated with medication, to measure the CVD risk in family caregivers of PWD.³⁷

Several studies also applied plasma indicators as biomarkers for showing cardiovascular status. The resting plasma norepinephrine (NE) level predicts incident cardiovascular events in patients with end-stage renal disease,³⁸ and it was applied in

two cross-sectional studies.^{39,40} Seven studies used IL-6 and DD levels to evaluate the risk of CVD. Carotid intima-media thickness (IMT), a marker of subclinical atherosclerosis,⁴¹ was applied in a cross-sectional study.⁴²

Modifiable associated factors of CVD risk

Stress and depressive symptoms. Stress and depressive symptoms were modifiable associated factors of CVD risk among family caregivers of PWD. Daily stressors were positively related to an elevation of IL-6 ($p=0.04$) and CRP ($p=0.04$) levels in Gouin et al.'s study.⁴³ Similar findings suggested that speech stress significantly increased HR ($p=0.017$), systolic BP ($p=0.002$), and diastolic BP ($p<0.001$) among spousal Alzheimer caregivers as reported by Von Känel et al.'s research team in cohort studies.²⁴ Mausbach et al.⁴⁴ also found that after adjusting for sociodemographic and health risk factors in a cohort study, greater depressive symptoms ($p=0.04$) and distress from problem behavior of patients ($p=0.03$) were significant predictors of incident CVD diagnoses. A significant decrease in the number of MetS factors after nursing home placement of the spouse only occurred in caregivers

with lower levels of depressive symptoms ($p=0.01$).³⁶ Additionally, the number of negative life events, which are positively associated with stress, also predict higher plasma DD levels ($p=0.01$).^{31,45}

Pleasant leisure activity. Three reviewed studies showed that engagement of pleasant leisure activities (e.g., watching TV, going on outings, shopping or buying things, having coffee, tea, etc. with friends) was likely to reduce the CVD risk in family caregivers of PWD. In Mausbach et al.'s⁴⁴ study, greater engagement in pleasant leisure activities predicted reduced mean arterial BP (MAP) ($p=0.04$) and reduced diastolic BP ($p=0.03$) over 5 years. This positive effect of pleasant leisure activities on physical health among caregivers was also found by Chattillion and colleagues.⁴⁶ In their study, participants with high engagement in pleasant events plus low perceived social and recreational activity restriction (AR) (being restricted from engaging in activities, such as going shopping, visiting friends, working on hobbies) had significantly lower MAP compared with those with low pleasure plus high restriction ($p=0.01$) and those with high pleasure plus high restriction or low pleasure plus low restriction ($p=0.023$). Another study showed that the duration of caregiving was significantly associated with epinephrine levels when social and recreational AR was high ($p=0.008$), but not when AR was low ($p=0.799$).³⁹

Coping self-efficacy and coping strategy. Two studies showed that family caregivers with higher levels of coping self-efficacy had a lower risk of CVD.^{47,48} High levels of self-efficacy for problem-focused coping were associated with lower MAP and systolic BP.⁴⁹ Self-efficacy further buffered the relationship between risk factors and CVD risk. In Mausbach et al.'s⁵⁰ study (2007), when self-efficacy was low, stress was significantly

related to IL-6 levels ($\beta=0.43$). However, when self-efficacy was high, stress was no longer significantly related to IL-6 levels ($\beta=-0.10$). Coping strategy was associated with CVD risk among family caregivers of PWD in the two following studies. Active coping was shown to be negatively related with diastolic BP ($p<0.01$),⁴⁹ and similarly, greater avoidance in coping was related to a greater level of BP reactivity ($p<0.001$).¹³

Physical activity and social support. Physical activity also moderated cardiometabolic risk in caregivers in one study. Among participants with low levels of physical activity, caregivers had greater cardiometabolic risk scores than did non-caregivers ($p=0.017$); there was no group difference in participants with high levels of physical activity ($p=0.81$).³⁵ Furthermore, social support moderated the CVD risk in family caregivers of PWD and systolic BP did not vary as a function of age in subjects with relatively high levels of social support.¹²

Sleep conditions. Whether the sleep conditions of family caregivers of PWD have an effect on their cardiovascular reactivity is debatable. In Schwartz et al.'s cross-sectional study, nighttime sleep duration, the percentage of time spent sleeping at night, and daytime naps were not significantly associated with the likelihood of having hypertension (odds ratio [OR], 0.97; 95% confidence interval [CI], 0.62–1.52; OR, 1.02; 95% CI, 0.93–1.11; OR, 1.10; 95% CI, 0.44–2.74, respectively).³³ However, Mausbach and colleagues⁴⁰ (2006) found that after controlling for the number of cardiovascular risk factors (e.g., age, sex, BP, body mass index), increased awake time after sleep onset was positively associated with NE levels ($p=0.020$) and plasma DD levels ($p=0.038$).

Non-modifiable associated factors of CVD risk

Caregiving status and duration. Caregiving status is a significant non-modifiable factor associated with the risk of CVD. Four longitudinal studies reported that the risk of developing CVD was significantly higher among people who were caregivers of PWD compared with non-caregivers.^{24,36,50,51} Shaw et al.²⁰ (1999) found that caregivers of PWD were 67% more likely to develop hypertension than non-caregivers. In Von Känel et al.'s³⁷ study, spousal caregivers of PWD had higher Framingham coronary heart disease risk scores compared with non-caregivers. Other studies also showed some molecular and cellular changes, which may explain the increased risk of CVD in family caregivers of PWD.^{32,43} Longitudinal studies have also reported that both DD⁵² and IL-6⁵¹ levels were significantly increased over time in family caregivers of PWD. Another study showed that accumulation of IL-6 levels in caregivers was approximately four times higher than that in non-caregivers.⁵¹ After nursing home placement of patients, the risk of CVD was significantly reduced.³⁶

A study showed that, when caregiving ended, after the death of the spouse, the number of MetS factors was significantly reduced ($p=0.003$) and was no longer different from that of non-caregivers.³⁶ The duration of caregiving also increases the risk of developing CVD. Wu et al.¹⁴ showed significant impairment of cardiovascular baroreflex sensitivity, which was negatively associated with the CVD risk in long-term caregivers (caregiving ≥ 4 years) compared with short-term caregivers (caregiving < 4 years). Another study reported that the duration of caregiving was significantly positively associated with epinephrine levels, which were positively connected with NE levels ($p=0.008$).³⁹ A cross-sectional study conducted by Roepke and

colleagues⁴² also showed that the duration of care was positively associated with IMT of the carotid artery ($p=0.044$).

Other factors that may increase the risk of CVD in family caregivers of PWD are TT genes, sex, and race. In one study, the TT genotype was associated with more adverse levels of waist circumference ($p=0.026$), triglycerides ($p=0.001$), and HDL cholesterol ($p=0.001$) in caregivers, which indicated that the TT genotype was associated with a higher risk of CVD.⁵³ Four studies reported that African American caregivers were at higher risk of suffering from hypertension and CVD than Caucasians.^{30,49,54,55} One study also showed that female caregivers showed greater systolic BP and diastolic BP reactivity to a laboratory-based stress task (i.e., discussing caregiving difficulties) compared with male caregivers ($p \leq 0.01$).⁵⁶ This finding suggests that female caregivers experience greater BP reactivity to caregiving-related stress than do male caregivers.

Discussion

The results of this systematic review showed 10 factors that were associated with the risk of CVD in 3689 family caregivers of PWD. These factors were sex, genes, race, caregiving status, duration of caregiving, stress and depressive symptoms, negative life events, self-efficacy, coping strategy, engagement in pleasant activity, and physical activity. Identifying and understanding the risk factors before implementing interventions is important. This protects caregivers from the negative consequences of caregiving tasks.

In this review, four studies showed that caregivers experienced a higher risk of CVD than did non-caregivers.^{24,36,50,51} A long duration of caregiving (> 4 years) is likely to increase the risk of CVD among caregivers. Additionally, female caregivers, older caregivers, and African American

caregivers have a higher risk of developing CVD than their counterparts. Even though caregiving conditions, sex, age, and race cannot be changed, there are other ways of decreasing the risk of CVD in family caregivers of PWD. These methods include reducing stress, improving self-efficacy and coping strategies, promoting leisure activities, increasing physical activity, and providing more social support.

Six studies that were included in this review showed that psychological stress and depressive symptoms were likely to increase the risk of CVD in family caregivers of PWD.^{31,43–45,48,57} Prospective studies that were conducted in initially healthy adults supported the positive relationship between long-term stress and CVD morbidity and mortality.^{58,59} The positive relationship between the number of recent negative life-events and CVD risk, and the positive relationship between stress and CVD risk^{31,45} were well established in these studies. Family caregivers normally experience a higher level of stress than do non-caregivers.^{60–62} Reducing stress is not only beneficial for psychological health, but also helpful for physical health in family caregivers of PWD. Therefore, reducing stress is at the top of the agenda in family caregivers of PWD.

Self-efficacy is negatively related to depressive symptoms in family caregivers of PWD.⁶³ Improvement of self-efficacy has the potential to reduce BP in family caregivers of PWD.⁴⁷ Self-efficacy is an individual's assessment of his or her ability to successfully master a specific task.⁶⁴ Coping self-efficacy is a form of self-efficacy, which is relevant to caregivers, because it relates to the degree to which they believe they can carry out the tasks that are necessary to cope with a challenge.⁶⁵ Bandura et al.⁶⁶ demonstrated that high levels of coping self-efficacy were able to reduce BP and cardiometabolic reactivity in the short term. Coping

self-efficacy is likely to moderate the negative effects of stress on CVD in family caregivers of PWD.⁴⁸ Stressed caregivers who experience a higher level of self-efficacy are at lower risk of CVD.⁴⁸ This similar condition also occurs at different levels of AR. The duration of caregiving is significantly positively related to cardiac risk when social and recreational AR is high, but not when AR is low.³⁹ Therefore, clinicians should make the effort to conduct psychological counselling and psychotherapy to improve self-efficacy in family caregivers of PWD periodically. Furthermore, decreasing social and recreational AR, as well as increasing pleasant leisure activities, are required to reduce the risk of CVD in caregivers.

Increasing engagement in pleasant leisure activities has the ability to reduce stress and CVD risk in family caregivers of PWD.^{22,46} This finding was also proven by a randomized, controlled trial as follows. Moore and colleagues⁶⁷ performed a behavioral activation intervention, which aimed to increase engagement in pleasurable activities and then to decrease the depressive symptoms and CVD risk (IL-6) in family caregivers of PWD. Caring for relatives with dementia may increase family caregivers' perception of not being able to have sufficient time and energy to engage in social and recreational activities, thus increasing their depressive symptoms.^{68,69} Increasing participation in pleasurable events is the main component of cognitive-behavior therapy, and enhancing positive activities (i.e., behavioral activation) effectively reduces depressive symptoms in different types of people, including caregivers.^{70–72} Implementing interventions to increase the engagement of pleasurable activities is likely to produce positive results for family caregivers of PWD.

Physical activity clearly reduces the risk of CVD among the general population.⁷³ The World Health Organization has

pointed out that participation in moderate physical activity (e.g., brisk walking, dancing, caring/moving moderate loads [<20 kg] for 150 minutes each week [or equivalent]) is estimated to reduce the risk of ischemic heart disease by approximately 30%.^{74,75} For family caregivers of PWD, performing physical activity can also decrease the risk of CVD.³⁵ A study showed that an intervention of moderate-intensive physical activity (four 30- to 40-minute exercise sessions per week of primarily home-based brisk walking) significantly reduced BP in female family caregivers of PWD compared with those who were provided with nutritional education.⁷⁶ Performing physical activity can decrease the risk of CVD and lower stress in caregivers of PWD.^{76,77} Perceived stress in female caregivers of PWD was significantly reduced by telephone-based exercise intervention.⁷⁷ However, caregivers were reported to perform less physical activity than non-caregivers.^{35,78} Finding solutions to increase physical activity of family caregivers of PWD is important. Family caregivers can achieve a great benefit of performing physical activity to improve their physical and psychological health.

This is the first study to review the factors that are associated with CVD risk in family caregivers of PWD. Compared with risk factors of CVD in non-caregivers, factors that are associated with CVD risk in family caregivers of PWD are focused more on psychological aspects (Table 2). There are similar risk factors of CVD among caregivers and non-caregivers alike, such as physical inactivity and depression. However, researchers have previously focused their attention on psychological effects, such as AR and self-efficacy on CVD risk in family caregivers of PWD.

This review has several limitations. First, this review only included studies that were written in English. Studies that were written in other languages were excluded.

Therefore, risk factors of CVD in family caregivers in other non-English speaking countries may not have been fully represented in this review. Second, this review aimed to examine risk factors of CVD in family caregivers of PWD. Therefore, only cross-sectional and longitudinal studies were included. The causal relationship between risk factors and the risk of CVD needs to be further confirmed in randomized, controlled trials. Third, to improve the effect of interventions, understanding the mechanisms between caregiving situation-related factors and CVD risk is important. Without knowing the mediating effect, developing an appropriate intervention will not be possible. Even though this review reported some moderating factors (e.g., self-efficacy and AR) between stress and the risk of CVD, the mediating effect should be investigated further. An example of this effect is that family functioning is significantly associated with psychological distress in family caregivers of PWD, and partially mediates the relationship between objective burden and psychological distress.⁷⁹ Therefore, further study could investigate the relationship between family functioning and the risk of CVD in family caregivers of PWD, and then develop appropriate interventions accordingly. Fourth, various measures of CVD risk were included in this review, which limited the consistency of the study results. Many CVD guidelines have recommended some forms of risk scoring for planning primary prevention interventions.⁸⁰⁻⁸² However, physicians' attitudes towards CVD risk assessment, economic issues, challenges when communicating with patients, and patients' understanding of risk affect the selection of assessment tools. Therefore, all studies are unlikely to choose the same measurement of CVD risk in family caregivers of PWD. However, future studies should consider whether their assessment

is comprehensive enough to measure the risk of CVD.

Implication for future research and clinical practice

Family caregivers of PWD experience a higher risk of developing CVD compared with non-caregivers. Psychological and physical interventions have shown a promising probability of improving CVD and psychological stress in family caregivers of PWD. Further interventional studies should investigate whether the risk of CVD can be significantly reduced after decreasing the risk factors. More comprehensive interventional studies are required to examine what type of intervention is more effective in decreasing the risk of CVD, as well as psychological stress in family caregivers of PWD. More longitudinal studies should also be performed to investigate the causal relationships between other factors (instead of caregiving status) and CVD risk in family caregivers of PWD.

To decrease the risk of developing CVD in family caregivers of PWD, psychologists and psychotherapists are required to help family caregivers to decrease their stress level and depressive symptoms. Psychologists and psychotherapists could also help caregivers to adopt ways of improving their self-efficacy, such as providing cognitive-behavior therapy and other psychological and psychosocial intervention (e.g., educational interventions, individual coping strategies, supportive therapy).⁸³ Social and clinical workers could also use behavioral activation intervention⁸⁴ and leisure education⁸⁵ to promote pleasant leisure activities among family caregivers of PWD, and thus reduce CVD risk among them. Additionally, physical activity programs⁸⁶ should be provided to family caregivers to reduce their risk of developing CVD.

Support for the findings of this systematic review is likely to encourage new approaches to promote techniques focused on reducing the risk of CVD and to lessen the negative health consequences associated with caring for a family member with dementia over a long period of time.


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References

1. World Health Organization. Mental Health, http://www.who.int/mental_health/neurology/dementia/en/ (2017, accessed 2 January 2018).
2. World Health Organization. China: Improving home care for dementia patients, <http://www.who.int/features/2014/china-dementia-patients/en/> (2017, accessed 14 January 2018).
3. Brodaty H and Donkin M. Family caregivers of people with dementia. *Dialogues Clin Neurosci* 2009; 11: 217.
4. Pinquart M and Sörensen S. Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. *Psychol Aging* 2003; 18: 250.
5. Vitaliano PP, Zhang J and Scanlan JM. Is caregiving hazardous to one's physical health? A meta-analysis. *Psychol Bull* 2003; 129: 946.
6. Pinquart M and Sörensen S. Correlates of physical health of informal caregivers: a

- meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2007; 62: P126–P137.
7. Torti FM Jr, Gwyther LP, Reed SD, et al. A multinational review of recent trends and reports in dementia caregiver burden. *Alzheimer Dis Assoc Disord* 2004; 18: 99–109.
 8. Fredman L, Cauley JA, Satterfield S, et al. Caregiving, mortality, and mobility decline: the health, aging, and body composition (Health ABC) study. *Arch Intern Med* 2008; 168: 2154–2162.
 9. McCurry SM, Logsdon RG, Teri L, et al. Sleep disturbances in caregivers of persons with dementia: contributing factors and treatment implications. *Sleep Med Rev* 2007; 11: 143–153.
 10. Rullier L, Lagarde A, Bouisson J, et al. Psychosocial correlates of nutritional status of family caregivers of persons with dementia. *Int Psychogeriatr* 2014; 26: 105–113.
 11. Schwartz J. Sleep and markers of cardiovascular disease risk in elderly Alzheimer's caregivers. PhD Thesis, University of California, San Diego, USA, 2013.
 12. Uchino BN, Kiecolt-Glaser JK and Cacioppo JT. Age-related changes in cardiovascular response as a function of a chronic stressor and social support. *J Pers Soc Psychol* 1992; 63: 839–846.
 13. Vitaliano PP, Russo JB, Young SL, et al. Psychosocial factors associated with cardiovascular reactivity in older adults. *Psychosom Med* 1993; 55: 164–177.
 14. Wu KK, Bos T, Mausbach BT, et al. Long-term caregiving is associated with impaired cardiovagal baroreflex. *J Psychosom Res* 2017; 103: 29–33.
 15. World Health Organization. Cardiovascular diseases, <http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiocvascular-diseases> (2017, accessed 5 January 2018).
 16. Lee S, Colditz GA, Berkman LF, et al. Caregiving and risk of coronary heart disease in U.S. women: a prospective study. *Am J Prev Med* 2003; 24: 113–119.
 17. Cohen S, Janicki-Deverts D and Miller GE. Psychological stress and disease. *JAMA* 2007; 298: 1685–1687.
 18. Ory MG, Hoffman RR III, Yee JL, et al. Prevalence and impact of caregiving: a detailed comparison between dementia and nondementia caregivers. *The Gerontologist* 1999; 39: 177–186.
 19. Kim Y and Schulz R. Family caregivers' strains: comparative analysis of cancer caregiving with dementia, diabetes, and frail elderly caregiving. *J Aging Health* 2008; 20: 483–503.
 20. Shaw WS, Patterson TL, Ziegler MG, et al. Accelerated risk of hypertensive blood pressure recordings among Alzheimer caregivers. *J Psychosom Res* 1999; 46: 215–227.
 21. Márquez-González M, Cabrera I, Losada A, et al. Attentional avoidant biases as mediators in the association between experiential avoidance and blood pressure in dementia family caregivers. *Aging Ment Health* 2018; 22: 669–677.
 22. Mausbach BT, Romero-Moreno R, Bos T, et al. Engagement in pleasant leisure activities and blood pressure: a 5-year longitudinal study in Alzheimer caregivers. *Psychosom Med* 2017; 79: 735–741.
 23. Sowers JR, Epstein M and Frohlich ED. Diabetes, hypertension, and cardiovascular disease. *Hypertension* 2001; 37: 1053–1059.
 24. von Känel R, Dimsdale JE, Adler KA, et al. Exaggerated plasma fibrin formation (D-dimer) in elderly Alzheimer caregivers as compared to noncaregiving controls. *Gerontology* 2005; 51: 7–13.
 25. von Kanel R, Dimsdale JE, Mills PJ, et al. Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. *J Gerontol A Biol Sci Med Sci* 2006; 61: 963–969.
 26. Maggio M, Guralnik JM, Longo DL, et al. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol A Biol Sci Med Sci* 2006; 61: 575–584.
 27. Danesh J, Whincup P, Walker M, et al. Fibrin D-dimer and coronary heart disease. *Circulation* 2001; 103: 2323–2327.
 28. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383–394.

29. National Institute of Health. Quality assessment tool for observational cohort and cross-sectional studies: 2014, <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort> (2014, accessed 5 January 2018).
30. Wilcox S, Bopp M, Wilson DK, et al. Race differences in cardiovascular and cortisol responses to an interpersonal challenge in women who are family caregivers. *Ethn Dis* 2005; 15: 17–24.
31. von Känel R, Dimsdale JE, Patterson TL, et al. Acute procoagulant stress response as a dynamic measure of allostatic load in Alzheimer caregivers. *Ann Behav Med* 2003; 26: 42–48.
32. Laks J, Goren A, Dueñas H, et al. Caregiving for patients with Alzheimer's disease or dementia and its association with psychiatric and clinical comorbidities and other health outcomes in Brazil. *Int J Geriatr Psychiatry* 2016; 31: 176–185.
33. Schwartz J, Allison MA, Ancoli-Israel S, et al. Sleep, type 2 diabetes, dyslipidemia, and hypertension in elderly Alzheimer's caregivers. *Arch Gerontol Geriatr* 2013; 57: 70–77.
34. Hoshino J, Hori Y, Kondo T, et al. Characteristics of hypertension-related factors in female home caregivers in Japan—comparison with general community non-caregivers. *J Clin Nurs* 2013; 22: 466–478.
35. von Kanel R, Mausbach BT, Dimsdale JE, et al. Regular physical activity moderates cardiometabolic risk in Alzheimer's caregivers. *Med Sci Sports Exerc* 2011; 43: 181–189.
36. von Känel R, Mausbach BT, Dimsdale JE, et al. Cardiometabolic effects in caregivers of nursing home placement and death of their spouse with Alzheimer's disease. *J Am Geriatr Soc* 2011; 59: 2037–2044.
37. Von Känel R, Mausbach BT, Patterson TL, et al. Increased Framingham Coronary Heart Disease Risk Score in dementia caregivers relative to non-caregiving controls. *Gerontology* 2008; 54: 131–137.
38. Zoccali C, Mallamaci F, Parlongo S, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 2002; 105: 1354–1359.
39. Ho JS, Bordon J, Wang V, et al. Reduced activity restriction buffers the relations between chronic stress and sympathetic nervous system activation. *J Gerontol B Psychol Sci Soc Sci* 2014; 69: 408–416.
40. Mausbach BT, Ancoli-Israel S, von Kanel R, et al. Sleep disturbance, norepinephrine, and D-dimer are all related in elderly caregivers of people with Alzheimer disease. *Sleep* 2006; 29: 1347–1352.
41. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness. *Circulation* 2007; 115: 459–467.
42. Roepke SK, Allison M, Von Känel R, et al. Relationship between chronic stress and carotid intima-media thickness (IMT) in elderly Alzheimer's disease caregivers. *Stress* 2012; 15: 121–129.
43. Gouin JP, Glaser R, Malarkey WB, et al. Chronic stress, daily stressors, and circulating inflammatory markers. *J Health Psychol* 2012; 31: 264–268.
44. Mausbach BT, Patterson TL, Rabinowitz YG, et al. Depression and distress predict time to cardiovascular disease in dementia caregivers. *Health Psychol* 2007; 26: 539–544.
45. von Känel R, Dimsdale JE, Patterson TL, et al. Association of negative life event stress with coagulation activity in elderly Alzheimer caregivers. *Psychosom Med* 2003; 65: 145–150.
46. Chattillion EA, Ceglowski J, Roepke SK, et al. Pleasant events, activity restriction, and blood pressure in dementia caregivers. *Health Psychol* 2013; 32: 793–801.
47. Harmell AL, Mausbach BT, Roepke SK, et al. The relationship between self-efficacy and resting blood pressure in spousal Alzheimer's caregivers. *Br J Health Psychol* 2011; 16: 317–328.
48. Mausbach BT, von Känel R, Roepke SK, et al. Self-efficacy buffers the relationship between dementia caregiving stress and circulating concentrations of the proinflammatory cytokine interleukin-6. *Am J Geriatr Psychiatry* 2011; 19: 64–71.

49. Kim JH, Knight BG and Longmire CV. The role of familism in stress and coping processes among African American and White dementia caregivers: effects on mental and physical health. *Health Psychol* 2007; 26: 564–576.
50. Mausbach BT, von Känel R, Aschbacher K, et al. Spousal caregivers of patients with Alzheimer's disease show longitudinal increases in plasma level of tissue-type plasminogen activator antigen. *Psychosom Med* 2007; 69: 816–822.
51. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, et al. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *PNAS* 2003; 100: 9090–9095.
52. Mausbach BT, Aschbacher K, Patterson TL, et al. Effects of placement and bereavement on psychological well-being and cardiovascular risk in Alzheimer's caregivers: a longitudinal analysis. *J Psychosom Res* 2007; 62: 439–445.
53. Kring SII, Brummett BH, Barefoot J, et al. Impact of psychological stress on the associations between apolipoprotein E variants and metabolic traits: findings in an American sample of caregivers and controls. *Psychosom Med* 2010; 72: 427–433.
54. Knight BG, Longmire CVF, Dave J, et al. Mental health and physical health of family caregivers for persons with dementia: a comparison of African American and white caregivers. *Aging Ment Health* 2007; 11: 538–546.
55. Knight BG and McCallum TJ. Heart rate reactivity and depression in African-American and white dementia caregivers: reporting bias or positive coping? *Aging Ment Health* 1998; 2: 212–221.
56. Atienza AA, Henderson PC, Wilcox S, et al. Gender differences in cardiovascular response to dementia caregiving. *Gerontologist* 2001; 41: 490–498.
57. von Känel R, Dimsdale JE, Ziegler MG, et al. Effect of acute psychological stress on the hypercoagulable state in subjects (spousal caregivers of patients with Alzheimer's disease) with coronary or cerebrovascular disease and/or systemic hypertension. *Am J Cardiol* 2001; 87: 1405–1408.
58. Krantz DS and McCeney MK. Effects of psychological and social factors on organic disease: a critical assessment of research on coronary heart disease. *Annu Rev Psychol* 2002; 53: 341–369.
59. Kivimäki M, Virtanen M, Elovainio M, et al. Work stress in the etiology of coronary heart disease—a meta-analysis. *Scand J Work Environ Health* 2006: 431–442.
60. Schulz R and Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. *Am J Geriatr Psychiatry* 2004; 12: 240–249.
61. Covinsky KE, Newcomer R, Fox P, et al. Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. *J Gen Intern Med* 2003; 18: 1006–1014.
62. Ornstein K, Gaugler JE, Zahodne L, et al. The heterogeneous course of depressive symptoms for the dementia caregiver. *Int J Aging Hum Dev* 2014; 78: 133–148.
63. Gilliam C and Steffen A. The relationship between caregiving self-efficacy and depressive symptoms in dementia family caregivers. *Aging Ment Health* 2006; 10: 79–86.
64. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev* 1977; 84: 191.
65. Chesney MA, Neilands TB, Chambers DB, et al. A validity and reliability study of the coping self-efficacy scale. *Br J Health Psychol* 2006; 11: 421–437.
66. Bandura A, Reese L and Adams NE. Microanalysis of action and fear arousal as a function of differential levels of perceived self-efficacy. *J Pers Soc Psychol* 1982; 43: 5.
67. Moore RC, Chattillion EA, Ceglowski J, et al. 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). *Behav Res Ther* 2013; 51: 623–632.
68. Williamson GM and Schulz R. Activity restriction mediates the association between pain and depressed affect: a study of younger and older adult cancer patients. *Psychol Aging* 1995; 10: 369.
69. Williamson GM and Shaffer DR. The activity restriction model of depressed affect.

- In: Williamson GM, Shaffer DR and Parmelee PA (eds) *Physical illness and depression in older adults*. 1st ed. Dordrecht: Springer, 2002, pp. 173–200.
70. Cuijpers P, Van Straten A and Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. *Clin Psychol Rev* 2007; 27: 318–326.
 71. Thompson LW. Cognitive-behavioral therapy and treatment for late-life depression. *J Clin Psychiatry* 1996; 57: 29–37.
 72. Coon DW, Thompson L, Steffen A, et al. Anger and depression management: psycho-educational skill training interventions for women caregivers of a relative with dementia. *Gerontologist* 2003; 43: 678–689.
 73. Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 2002; 347: 716–725.
 74. World Health Organization. Cardiovascular diseases-Data and statistics, <http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cardiovascular-diseases/data-and-statistics> (2017, accessed 7 February 2019).
 75. World Health Organization. What is moderate-intensity and vigorous-intensity physical activity? http://www.who.int/dietphysicalactivity/physical_activity_intensity/en/ (2017, accessed 7 February 2019).
 76. Castro CM, Wilcox S, O'sullivan P, et al. An exercise program for women who are caring for relatives with dementia. *Psychosom Med* 2002; 64: 458–468.
 77. Connell CM and Janevic MR. Effects of a telephone-based exercise intervention for dementia caregiving wives: a randomized controlled trial. *J Appl Gerontol* 2009; 28: 171–194.
 78. Fredman L, Bertrand RM, Martire LM, et al. Leisure-time exercise and overall physical activity in older women caregivers and non-caregivers from the Caregiver-SOF Study. *Prev Med* 2006; 43: 226–229.
 79. Mitrani VB, Lewis JE, Feaster DJ, et al. The role of family functioning in the stress process of dementia caregivers: a structural family framework. *The Gerontologist* 2006; 46: 97–105.
 80. Pearson TA, Blair SN, Daniels SR, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. *Circulation* 2002; 106: 388–391.
 81. Rabar S, Harker M, O'flynn N, et al. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *Br Med J* 2014; 349: g4356.
 82. World Health Organization. Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. https://www.who.int/nmh/publications/essential_ncd_interventions_lr_settings.pdf (2010, accessed 20 March 2019)
 83. Selwood A, Johnston K, Katona C, et al. Systematic review of the effect of psychological interventions on family caregivers of people with dementia. *J Affect Disord* 2007; 101: 75–89.
 84. Losada A, Márquez-González M and Romero-Moreno R. Mechanisms of action of a psychological intervention for dementia caregivers: effects of behavioral activation and modification of dysfunctional thoughts. *Int J Geriatr Psychiatry* 2011; 26: 1119–1127.
 85. Carbonneau H, Caron CD and Desrosiers J. Effects of an adapted leisure education program as a means of support for caregivers of people with dementia. *Arch Gerontol Geriatr* 2011; 53: 31–39.
 86. Farran CJ, Staffileno BA, Gilley DW, et al. A lifestyle physical activity intervention for caregivers of persons with Alzheimer's disease. *Am J Alzheimers Dis Other Demen* 2008; 23: 132–142.
 87. Grundy SM. Cholesterol and coronary heart disease: a new era. *JAMA* 1986; 256: 2849–2858.
 88. Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. *Am J Med* 1977; 62: 707–714.

89. Kannel WB and McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979; 241: 2035–2038.
90. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996; 275: 1571–1576.
91. Musselman DL, Evans DL and Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998; 55: 580–592.
92. Lee KS, Park CY, Meng KH, et al. The association of cigarette smoking and alcohol consumption with other cardiovascular risk factors in men from Seoul, Korea. *Ann Epidemiol* 1998; 8: 31–38.
93. Lakka T and Bouchard C. Physical activity, obesity and cardiovascular diseases. In: von Eckardstein A *Atherosclerosis: diet and drugs*. 1st ed. Berlin, Heidelberg: Springer, 2005, pp. 137–163.
94. Shaw WS, Patterson TL, Semple SJ, et al. Emotional expressiveness, hostility and blood pressure in a longitudinal cohort of Alzheimer caregivers. *J Psychosom Res* 2003; 54: 293–302.