



Poor caregiver mental health predicts mortality of patients with neurodegenerative disease

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Dementia and other neurodegenerative diseases cause profound declines in functioning; thus, many patients require caregivers for assistance with daily living. Patients differ greatly in how long they live after disease onset, with the nature and severity of the disease playing an important role. Caregiving can also be extremely stressful, and many caregivers experience declines in mental health. In this study, we investigated the role that caregiver mental health plays in patient mortality. In 176 patient-caregiver dyads, we found that worse caregiver mental health predicted greater patient mortality even when accounting for key risk factors in patients (i.e., diagnosis, age, sex, dementia severity, and patient mental health). These findings highlight the importance of caring for caregivers as well as patients when attempting to improve patients' lives.

neurodegenerative disease | dementia caregiving | mental health | mortality

Over 35 million adults worldwide have been diagnosed with dementia and other neurodegenerative diseases—disorders that lead to progressive declines in cognitive, emotional, and motor functioning (1). These declines cause many patients to rely on family members for caregiving, with estimates indicating that over 17 million Americans are providing unpaid care for an aging adult (2). Neurodegenerative diseases are inevitably fatal; however, individuals differ greatly in how long they live after their disease has been diagnosed. Research has underscored the important influence that patient factors (e.g., disease severity, age) have on patient mortality (3), but less attention has been given to the influence that caregivers have on patient mortality. Caregivers fulfill patients' essential needs, from helping them with activities of daily living (e.g., eating) to administering health directives and advocating for their care (4). This assistance is essential to patient outcomes, but it also takes a toll on the caregivers themselves. Many caregivers suffer from poor mental health (5), which may in turn shape the care patients receive (6). Thus, although patient-centered factors play an undeniably important role in patient mortality, caregiver-centered factors are also crucial to examine.

Patient Factors That Predict Mortality

In patients with neurodegenerative disease, survival after receiving a diagnosis can vary between 3 and 10 y, with average survival being under 5 y (7). A number of patient characteristics have been found to be associated with greater mortality, including male sex, later age of onset, poor mental health, disease subtype, and disease severity (8–10).

Caregiving as a Risk Factor for Poor Mental Health

Although some caregivers find caring for a patient with neurodegenerative disease to be rewarding and remain resilient to the stress of caregiving (11, 12), others find the experience to be extremely burdensome and develop significant physical and mental health problems (13). For example, caregivers suffer from depression at four times the rate of noncaregivers (14) and are almost three times as likely to seek treatment for anxiety (15). Caregivers can become increasingly socially isolated, and the subsequent decreases in social support are closely linked to worsening caregiver mental health (16).

Do Declines in Caregiver Mental Health Predict Patient Mortality?

Declines in caregiver mental health are a common outcome of caregiving. These declines, in turn, represent a plausible risk factor for patient mortality, given the crucial role that caregivers play in patients' lives. Caregiver mental health can influence patient mortality in several ways. First, worse mental health in caregivers can influence the quality of care they provide. For example, depressed caregivers are more likely to engage in patient neglect and abuse (6, 17), behaviors that are known to predict patient mortality (18). Second, caregiver mental health problems can weaken the social bond between patients and caregivers. For example, caregivers often report feeling lonely and isolated in their relationships (19). Low-quality relationship functioning has been linked to poorer physical health, impaired immune functioning, and mortality in relationship partners (20, 21). Finally, worse mental health in caregivers may negatively influence patients through emotion contagion or behavioral mimicry. Given that caregivers experience relatively high levels of stress (2, 22), and that stress-related expressions of negative affect and physiological arousal (e.g., cortisol levels) tend to be shared within relationship partners (23–26), it is possible that caregivers' subjective and physiological experience of stress may be transmitted to the patients in their care. Given that heightened stress has been linked with poor health and mortality (27–29), patients may in turn experience greater risks to their own health.

Significance

In this study, we investigated the role that caregiver mental health plays in patient mortality. In 176 patient-caregiver dyads, we found that worse caregiver mental health predicted greater patient mortality even when accounting for key risk factors in patients (i.e., diagnosis, age, sex, dementia severity, and patient mental health). Thus, although providing the best possible care for the large and growing number of individuals with neurodegenerative disease is an important public health priority, our findings suggest that these efforts should also consider caregiver mental health as an important intervention target. These findings represent research at the intersection of psychology, neuroscience, and medical science, and highlight the importance of caring for caregivers as well as patients when attempting to improve patients' lives.

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Present Study

The existing literature has established a number of patient factors that influence patient mortality, but relatively few studies have examined how caregiver factors influence patient mortality (30). Furthermore, no studies to our knowledge have examined whether caregiver mental health uniquely predicts patient mortality after accounting for relevant patient risk factors. The present study addressed this crucial gap in a sample of 176 caregivers and patients with a wide range of neurodegenerative diseases. We examined whether caregiver mental health predicted patient mortality above and beyond well-established patient risk factors (i.e., diagnosis, age, sex, dementia severity, patient mental health) and other caregiver characteristics that could influence mortality (e.g., caregiver physical health).

Methods

Participants. All study participants were recruited between 2007 and 2012 from the University of California (UC) San Francisco Memory and Aging Center (MAC), where they received diagnoses and clinical care. Patients were referred to the MAC by a number of sources including self-referrals, clinician referrals, and referrals through Alzheimer's Disease Research Centers. Given the MAC's expertise in neurodegenerative disease and ongoing research programs, referrals typically include less common neurodegenerative diseases subtypes (e.g., frontotemporal dementia). Thus, although patient recruitment was consecutive (resulting in a random sample), the distribution of diseases in our sample was somewhat different than that seen in typical memory clinics (Table 1).

At the MAC, patients were introduced to the dementia research project and, if interested, could opt into the study and be contacted by recruiters to schedule their research visits. Participants underwent standard neurological and psychological testing, assessment of cognitive and behavioral symptoms, and structural brain scans (MRI). This information was used to provide a diagnosis based on current criteria (see below). Participants diagnosed with a neurodegenerative disease who had a reliable informant were then consecutively recruited and given the option to opt into a separate laboratory session at the UC Berkeley Psychophysiology Laboratory (BPL) that was focused on assessing patients' and caregivers' social and emotional functioning (31). Prospective participants in the BPL assessment were informed that their participation was voluntary, their decision would have no effect on their medical treatment, and they could opt out from this aspect of the research at any time. Participants received no payment for the BPL session beyond reimbursement for lunch, transportation, and incidental expenses. Approximately 37% of MAC participants agreed to complete the laboratory visit at the BPL.

During the 5 y of this study, 176 patients and their familial caregivers were assessed at both the MAC and the BPL. Unless patients chose to opt out, patients were then followed at the MAC until death and, for those who consented, autopsy. In this sample, (i) 48 patients met diagnostic criteria for behavioral-variant frontotemporal dementia (bvFTD) (32), (ii) 20 for nonfluent variant primary progressive aphasia (nfvPPA), (iii) 31 for semantic variant primary progressive aphasia (svPPA) (33), (iv) 41 for Alzheimer's disease (AD) (34), (v) 19 for corticobasal syndrome (CBS) (35), and (vi) 17 for progressive supranuclear palsy (PSP) (36). Within the present sample, 85% of caregivers ($n = 149$) were spouses of the patient, whereas 8% were adult children ($n = 14$) and 7% were siblings ($n = 13$).

Procedure. During their comprehensive evaluations at the MAC, patient mental health and dementia severity were assessed by qualified clinicians. Before their BPL session, caregivers completed a questionnaire packet at home that contained a consent form (approved by the UC Berkeley Committee for the Protection of Human Subjects) and questionnaires measuring caregiver mental and physical health. About a week later, participants came to the BPL for the assessment of emotional functioning. Upon arrival, participants were informed that they would be participating in a study of emotion and that their physiological, behavioral, and self-reported responses would be recorded and videotaped. After completing another consent form (approved by the UC Berkeley Committee for the Protection of Human Subjects), patients and caregivers participated in the laboratory session. There were no follow-up sessions conducted at Berkeley; thus, the questionnaire packet completed before the laboratory session was the only time caregiver mental and physical health were assessed. Study materials and associated protocols are available upon request from the corresponding author.

Measures.

Patient mortality. Patients typically completed annual follow-up appointments at the MAC to monitor their disease severity and receive updated treatment plans. If patients were unable to return in person, updates were provided

over the telephone. When we learned that a patient had died, the date of death was acquired. Mortality data were not available for caregivers. Between the beginning of the study (January 2007) and the cutoff date used for the present analyses (May 1, 2016), 98 deaths occurred (55.7%). For patients who died, survival time was computed as the number of days between the date that patients participated in the BPL assessment and the date of death. For patients who were still alive, censor time was computed as the number of days between the date of the BPL assessment and the cutoff date (37).

Patient dementia severity. Patients' dementia severity was assessed using the Clinical Dementia Rating Scale Sum of Boxes (38), a clinician-rated scale designed to examine impairment across six domains: memory, orientation, judgment, community affairs, home and hobbies, and personal care. Each domain was rated on a 5-point scale: 0 = no impairment, 0.5 = questionable impairment, 1 = mild impairment, 2 = moderate impairment, and 3 = severe impairment. Each domain score was then summed to obtain Sum of Boxes scores. Scores range from 0 to 18, with higher scores indicating greater impairment.

Patient mental health symptoms. Trained clinicians conducted semistructured interviews with caregivers using the Neuropsychiatric Inventory (NPI) (39) to assess patients' behavioral and emotional symptoms. The NPI is designed to examine 12 domains: delusions, hallucinations, depression, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleep disturbances, and eating disorders. For each domain, frequency (1 = occasionally, less than once per week, to 4 = very frequently, once or more per day or continuously) and severity (1 = mild, to 3 = severe) were rated, and the total score for that domain was computed by multiplying frequency by severity. An overall score was computed by summing scores across the 12 domains. This overall score could range from 0 to 144, with higher scores indicating greater behavioral and emotional impairments.

Caregiver mental health symptoms. Familial caregivers of patients with neurodegenerative disease completed two measures of their own mental health symptoms, the Medical Outcomes Study Short-Form Survey (SF-36) (40), and the Symptom Checklist-90 Revised (SCL-90R) (41). The SF-36 is a 36-item self-report measure designed to assess eight domains: physical functioning, role limitations due to physical health, energy/fatigue, pain, general health problems, role limitations due to emotional problems, emotional well-being, and social functioning. Scores for each of these domains range from 0 (worst) to 100 (best). According to convention, summed scores from each of the eight domains were z scored and then weighted to create a composite measure of mental health such that mental health subscales were weighted more heavily (42). Composite scores were then multiplied by -1 so that higher scores indicated worse caregiver mental health symptoms. The SCL-90R is a 90-item questionnaire designed to assess symptoms of mental health in nine domains: depression, anxiety, hostility, somatization, obsessive-compulsivity, interpersonal sensitivity, phobic anxiety, paranoid ideation, and psychoticism. Each item was rated on a 5-point scale of distress (0 = not at all, to 4 = extremely). The SCL-90R Global Severity Index score is the mean score of all items, with higher scores indicating greater overall psychological distress.

Caregiver physical illness symptoms. Caregiver physical illness was assessed using the SF-36, described above. According to convention, summed scores from each of the eight domains measured by the SF-36 (see above) were z scored and weighted to create a composite measure of physical health (such that physical health subscales were weighted more heavily).

Results

Data Analytic Approach. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and survival curves for patient mortality. Analyses proceeded in three steps. First, we tested whether patient variables (i.e., diagnosis, sex, age, dementia severity, patient mental health) predicted patient mortality (model 1). Because diagnosis was a multilevel categorical variable, all diagnoses were dummy-coded (0 = absent; 1 = present): bvFTD, nfvPPA, svPPA, AD, and CBS. PSP was set as the reference group because patients with neurodegenerative diseases that affect movement and autonomic nervous centers (e.g., PSP), generally do not live as long as those with diseases that impact higher-order abilities such as cognition and emotion (e.g., AD and bvFTD) (43). All other variables were entered as continuous variables. Second, we tested whether caregiver mental health symptoms predicted patient mortality (model 2). To examine the robustness of these findings, we replicated these analyses using the two measures of caregiver mental health symptoms: the SF-36 (40) and the SCL-90R (41). Third, we tested whether caregiver mental health symptoms uniquely predicted patient mortality by including patient

Table 1. Descriptive statistics (means, SDs) for patient and caregiver variables

Variable	Neurodegenerative disease subtype					
	bvFTD	nfvPPA	svPPA	AD	CBS	PSP
Sample size	48	20	31	41	19	17
Patient						
Sex, % male	69	50	45	49	47	53
Age	61.5 (8.14)	67.9 (7.58)	63.6 (5.51)	61.7 (8.62)	66.4 (5.58)	68.3 (5.78)
Dementia severity	7.00 (3.16)	2.33 (2.07)	4.44 (2.86)	4.50 (2.13)	4.24 (3.39)	5.15 (2.79)
Mental health symptoms	42.5 (21.03)	15.7 (13.18)	33.4 (22.03)	21.8 (23.06)	22.0 (22.19)	28.4 (15.61)
Caregiver						
Sex, % male	35	45	55	42	47	41
Age	59.4 (12.35)	67.0 (14.37)	61.5 (14.79)	60.3 (7.14)	61.3 (10.74)	63.1 (8.71)
Mental health symptoms						
SF-36	0.68 (1.12)	0.08 (0.93)	-0.13 (0.95)	0.02 (1.05)	-0.17 (1.26)	0.41 (0.94)
SCL-90R	0.56 (0.36)	0.52 (0.44)	0.38 (0.30)	0.34 (0.23)	0.54 (0.71)	0.42 (0.47)
Physical health symptoms						
	-0.04 (1.02)	0.13 (0.96)	-0.13 (0.86)	-0.05 (0.80)	0.34 (1.30)	-0.16 (1.16)

Means (SD) are presented. AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; nfvPPA, nonfluent variant primary progressive aphasia; PSP, progressive supranuclear palsy; SCL-90R, Symptom Checklist-90 Revised; SF-36, Medical Outcomes Study Short-Form Survey; svPPA, semantic variant primary progressive aphasia. According to scale conventions, caregiver mental and physical health variables were weighted z-score averages.

variables (i.e., diagnosis, sex, age, dementia severity, mental health) and caregiver variables (i.e., mental and physical health symptoms) as simultaneous predictors of patient mortality (model 3). See *Supporting Information* for more information about all measures.

Patient Variables and Patient Mortality. As depicted in Table 2 (model 1), when testing whether patient variables (i.e., diagnosis, sex, age, dementia severity, mental health) predicted patients' mortality, two diagnosis subtypes predicted lower patient mortality relative to the reference group (i.e., patients with PSP): AD (HR = 0.35, 95% CI [0.167, 0.722], $P = 0.005$) and svPPA (HR = 0.14, 95% CI [0.054, 0.356], $P < 0.001$). Patient mental health symptoms predicted greater patient mortality (HR = 1.01, 95% CI [1.000, 1.019], $P = 0.047$). Patient sex, age, and dementia severity were not significant predictors of patient mortality (values of $P > 0.504$).

Caregiver Mental Health Symptoms and Patient Mortality. As depicted in Table 2 (model 2), worse caregiver mental health (as measured by elevated SF-36 symptom scores) was associated with greater patient mortality (HR = 1.47, 95% CI [1.225, 1.763], $P < 0.001$). To examine the robustness of these findings, we replicated these analyses with the second measure of caregiver mental health symptoms (SCL-90R). Results again indicated that worse caregiver mental health was associated with greater patient mortality (HR = 1.87, 95% CI [1.215, 2.871], $P = 0.004$).

Unique Association Between Caregiver Mental Health Symptoms and Patient Mortality. To examine the extent to which caregiver mental health uniquely predicted patient mortality, we included all patient variables (i.e., diagnosis, sex, age, dementia severity, patient mental health) as well as caregiver mental and physical health symptoms as simultaneous predictors in our model. As depicted in Table 2 (model 3), results revealed that caregiver

Table 2. Cox regression HRs (and 95% CIs) of patient and caregiver variables predicting patient mortality

Variable	HRs and 95% CIs		
	Model 1	Model 2	Model 3
Patient			
Diagnosis			
bvFTD	0.50 [0.245, 1.023]	—	0.52 [0.256, 1.060]
nfvPPA	0.76 [0.343, 1.701]	—	0.78 [0.349, 1.759]
AD	0.35 [0.167, 0.722]**	—	0.37 [0.174, 0.770]**
svPPA	0.14 [0.054, 0.356]***	—	0.16 [0.063, 0.419]***
CBS	1.02 [0.492, 2.094]	—	1.22 [0.583, 2.564]
PSP	—	—	—
Sex	0.95 [0.618, 1.445]	—	0.82 [0.532, 1.251]
Age	1.00 [0.970, 1.027]	—	1.01 [0.978, 1.040]
Dementia severity	1.02 [0.954, 1.099]	—	1.02 [0.954, 1.099]
Mental health symptoms	1.01 [1.000, 1.019]*	—	1.01 [0.996, 1.015]
Caregiver			
Mental health symptoms (SF-36)	—	1.47 [1.225, 1.763]***	1.49 [1.210, 1.822]***
Physical health symptoms (SF-36)	—	—	0.95 [0.773, 1.154]

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Each model predicts patient mortality as a function of patient variables (Model 1), as a function of caregiver mental health symptoms, as measured by the SF-36 (Model 2), or as a function of both patient and caregiver variables (Model 3). A dash (—) indicates that the given variable was not included within the model. For mental and physical health symptom measures, higher scores indicate worse symptoms. AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CBS, corticobasal syndrome; nfvPPA, nonfluent variant primary progressive aphasia; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia. Diagnosis was dummy coded, with PSP patients coded as the reference group.

mental health symptoms (measured with the SF-36) remained a significant predictor of patient mortality (HR = 1.49, 95% CI [1.210, 1.822], $P < 0.001$). This HR indicates that patient mortality was 1.49 times higher for each SD increase in caregiver mental health symptoms (see Fig. 1 for survival curves). This result also replicated when caregiver mental health was measured with the SCL-90R (HR = 1.60, 95% CI [1.011, 2.542], $P = 0.045$). These findings indicate that worse caregiver mental health is a unique predictor of patient mortality even when accounting for patient variables and caregiver physical health.

Discussion

The prevalence of neurodegenerative diseases is alarmingly high and is expected to increase with the growing aging population (44). Paralleling this rise in the number of patients is an increase in the number of caregivers who will be needed to provide critical assistance to patients across a broad range of areas. The present study aimed to understand the role that caregiver and patient factors play in patient mortality.

As expected, a number of aspects of patients' disease (i.e., diagnosis and mental health) predicted greater patient mortality. Results also revealed that low levels of caregiver mental health uniquely predicted greater patient mortality even when accounting for a number of risk factors in patients (i.e., diagnosis, sex, age, dementia severity, mental health) and other caregiver factors (i.e., caregiver physical health).

This finding raises the question of how poor caregiver mental health impacts patient mortality. Prior research has shown that lower caregiver mental health is associated with lower quality of care (6), which could in turn contribute to patient mortality in a number of ways (e.g., less awareness of patient health changes, poorer medication compliance, missing medical appointments). Lower caregiver mental health could also weaken the quality of the caregiver–patient relationship: damaged social bonds between relationship partners are known to predict worse health outcomes, even extending to risk for mortality (21). Finally, lower caregiver mental health could impact patient mental health through contagion of emotions (especially negative

emotions such as anger, fear, and sadness) or behavioral mimicry given that close others tend to share and reciprocate emotional experiences, expressions, and even physiological responses (23–26).

Providing the best possible care for the large and growing number of individuals with neurodegenerative disease is an important public health priority. Our findings suggest that these efforts should consider caregiver mental health as an important intervention target: In addition to the obvious benefits for caregivers, there could be benefits for patient longevity as well. Fortunately, there are a number of pharmacological and psychosocial interventions that are useful for treating depression, anxiety, and other mental health problems (e.g., cognitive behavioral therapy) (45, 46) in caregivers. Close monitoring of the mental health of caregivers of patients with neurodegenerative disease could lead to early interventions that would have maximal benefits for caregivers and for the patients in their care.

Strengths and Limitations. The research has several notable strengths. First, we examined a relatively large and well-powered sample of patients with multiple forms of neurodegenerative disease. The diagnoses of neurodegenerative disease were established using rigorous assessments that included neurological testing, neuropsychological testing, and structural neuroimaging to maximize diagnostic accuracy. This kind of sample provides greater confidence in the results and their generalizability across different forms of neurodegenerative disease, compared with prior investigations with small sample sizes and just one or two forms of neurodegenerative disease. Second, we used gold-standard measurements of both patient and caregiver variables to examine how both types of factors impact patient mortality. Prior research has rarely examined caregiver factors in addition to patient factors when examining patient health or mortality. Finally, we used multiple measures of caregiver mental health to ensure that the influence of caregiver mental health on patient mortality was robust.

The present study also has limitations that can be addressed with future research. First, it was not designed to test the mechanisms that link caregiver mental health with patient mortality. As discussed above, several mechanisms are possible, and future research that carefully assesses these mechanisms over time would help establish their possible mediating role in patient mortality. Although we have noted the causal role that caregiver mental health may have upon patient mortality, the inverse may also be true. That is, worse mental health in patients—which would likely hasten patient mortality—could promote worse caregiver mental health. The present study helps to rule out this alternative directionality by accounting for patient mental health, but this finding would be bolstered by future studies that assess patient health, caregiver health, and possible mediating mechanisms at multiple assessment points across time. Knowledge of these mechanisms would be extremely useful in designing experimental tests of the influence of caregiver mental health on patient mortality, and in planning clinical interventions to improve the lives of caregivers and patients.

Second, future research would benefit from considering possible moderators of the link between caregiver mental health and patient mortality. For example, the nature of the caregiver's relationship to the patient (e.g., spouse, child, sibling), or the availability of other family resources (e.g., social support), may influence how caregivers respond to the stress of caregiving and thus may influence the strength of the link between caregiver mental health and patient mortality. In future studies it would also be useful to examine other potential moderating influences (e.g., ethnicity, socioeconomic status, and education) to determine whether they increase or decrease patient vulnerability to lower caregiver mental health.

Third, future research would benefit from a more comprehensive assessment of patients' mental health to understand its possible role in patient mortality. In the present study, we used a well-validated (39) and widely used (47, 48) measure of patient

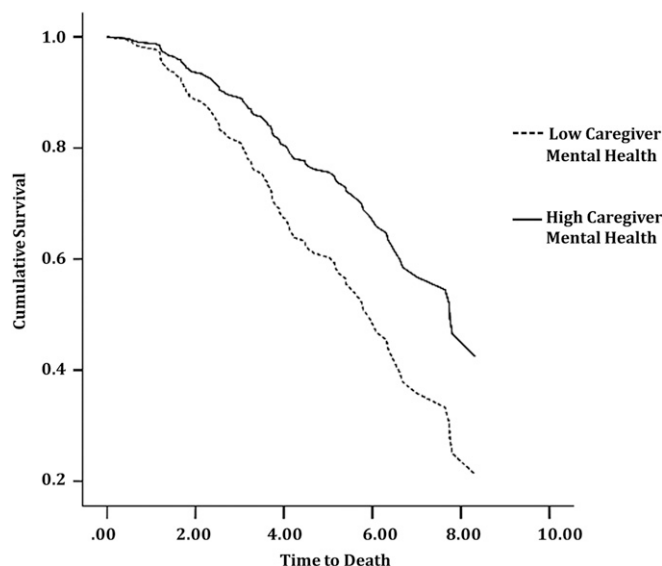


Fig. 1. Survival curves for caregiver mental health symptoms (SF-36) and patient mortality. The figure depicts survival curves for model 3 wherein caregiver mental health symptoms predict patients' survival rate while accounting for patient variables (i.e., diagnosis, sex, age, dementia severity, and mental health) and caregiver physical health. Caregiver mental health symptoms (as measured by the SF-36) are depicted using a median split for display purposes only.

mental health based on clinician ratings of caregiver reports; however, examining patients' own experiences—in addition to informant ratings of mental health—may provide important additional information on the role of patient mental health and patient insight in patient mortality.

Fourth, the sample of patients included in the present study was somewhat different from a sample that might be found in a typical memory clinic. For example, our sample of patients with AD was younger than average (mean age, 61.7 y) and more balanced in the proportion of male to female patients (49% males). This balance across genders is consistent with prior research suggesting that gender differences in AD typically do not emerge until participants are older than 85 y (49). Our sample also included patients with less common neurodegenerative disease subtypes (e.g., svPPA, CBS), which helped us determine whether our findings were consistent across diagnostic subtypes. For these reasons, it will be important for future research to replicate the present results using samples that more closely reflect the demographics observed in typical memory clinics.

Finally, it is important to note that living longer does not necessarily guarantee high quality of life. Although we did not directly measure patients' quality of life, we did assess their mental health—a crucial ingredient in quality of life (50). In our sample, better mental health in caregivers was associated with better mental health in patients ($r = 0.29$, $P < 0.001$). However, we do not know whether this association between caregiver

mental health and patient mental health remains stable over time. If it does, then the period of longer life in patients that was predicted by better caregiver mental health might be of good quality. This important issue can best be studied using longitudinal designs and more comprehensive assessments of patient quality of life. If this finding proves durable, it would further underscore the importance of determining whether interventions that aim to improve caregiver mental health also improve both the longevity and quality of life of patients with neurodegenerative disease. Tracking caregivers over time would also provide the opportunity to examine how caregiver mortality influences patient mortality.

Conclusion. Neurodegenerative diseases affect millions of people worldwide, and the numbers are rapidly growing. Unfortunately, cures have been elusive and current treatments are only mildly effective, leading many patients to become highly reliant on their caregivers. Caregiving for an individual with a neurodegenerative disease is an extremely challenging experience. The burden and stresses of caregiving create heightened risk for poor caregiver mental health, which contributes to greater mortality among patients. These findings thus highlight the importance of caring for caregivers (in addition to patients) when attempting to improve patients' lives.

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- Prince M, et al. (2013) The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimers Dement* 9:63–75.e2.
- Schulz R, Eden J (2016) *Families Caring for an Aging America* (The National Academies Press, Washington, DC).
- Todd S, Barr S, Roberts M, Passmore AP (2013) Survival in dementia and predictors of mortality: A review. *Int J Geriatr Psychiatry* 28:1109–1124.
- Black BS, et al. (2013) Unmet needs of community-residing persons with dementia and their informal caregivers: Findings from the maximizing independence at home study. *J Am Geriatr Soc* 61:2087–2095.
- Sørensen S, Duberstein P, Gill D, Pinquart M (2006) Dementia care: Mental health effects, intervention strategies, and clinical implications. *Lancet Neurol* 5:961–973.
- Wiglesworth A, et al. (2010) Screening for abuse and neglect of people with dementia. *J Am Geriatr Soc* 58:493–500.
- Fitzpatrick AL, Kuller LH, Lopez OL, Kawas CH, Jagust W (2005) Survival following dementia onset: Alzheimer's disease and vascular dementia. *J Neurol Sci* 229:230:43–49.
- Brodaty H, Seeher K, Gibson L (2012) Dementia time to death: A systematic literature review on survival time and years of life lost in people with dementia. *Int Psychogeriatr* 24:1034–1045.
- Wolfson C, et al.; Clinical Progression of Dementia Study Group (2001) A reevaluation of the duration of survival after the onset of dementia. *N Engl J Med* 344:1111–1116.
- Bang J, et al.; AL-108-231 Investigators (2016) Predicting disease progression in progressive supranuclear palsy in multicenter clinical trials. *Parkinsonism Relat Disord* 28:41–48.
- Harmell AL, Chattillion EA, Roepke SK, Mausbach BT (2011) A review of the psychobiology of dementia caregiving: A focus on resilience factors. *Curr Psychiatry Rep* 13:219–224.
- Andrén S, Elmståhl S (2005) Family caregivers' subjective experiences of satisfaction in dementia care: Aspects of burden, subjective health and sense of coherence. *Scand J Caring Sci* 19:157–168.
- Richardson TJ, Lee SJ, Berg-Weger M, Grossberg GT (2013) Caregiver health: Health of caregivers of Alzheimer's and other dementia patients. *Curr Psychiatry Rep* 15:367.
- Joling KJ, et al. (2010) Incidence of depression and anxiety in the spouses of patients with dementia: A naturalistic cohort study of recorded morbidity with a 6-year follow-up. *Am J Geriatr Psychiatry* 18:146–153.
- Kolanowski AM, Fick D, Waller JL, Shea D (2004) Spouses of persons with dementia: Their healthcare problems, utilization, and costs. *Res Nurs Health* 27:296–306.
- Brodaty H, Donkin M (2009) Family caregivers of people with dementia. *Dialogues Clin Neurosci* 11:217–228.
- Coyne AC, Reichman WE, Berbig LJ (1993) The relationship between dementia and elder abuse. *Am J Psychiatry* 150:643–646.
- Lachs MS, Williams CS, O'Brien S, Pillemer KA, Charlson ME (1998) The mortality of elder mistreatment. *JAMA* 280:428–432.
- Beeson RA (2003) Loneliness and depression in spousal caregivers of those with Alzheimer's disease versus non-caregiving spouses. *Arch Psychiatr Nurs* 17:135–143.
- Cacioppo JT, et al. (2002) Loneliness and health: Potential mechanisms. *Psychosom Med* 64:407–417.
- Robles TF, Kiecolt-Glaser JK (2003) The physiology of marriage: Pathways to health. *Physiol Behav* 79:409–416.
- Ory MG, Hoffman RR, 3rd, Yee JL, Tennstedt S, Schulz R (1999) Prevalence and impact of caregiving: A detailed comparison between dementia and nondementia caregivers. *Gerontologist* 39:177–185.
- Papp LM, Pendry P, Simon CD, Adam EK (2013) Spouses' cortisol associations and moderators: Testing physiological synchrony and connectedness in everyday life. *Fam Process* 52:284–298.
- Saxbe D, Repetti RL (2010) For better or worse? Coregulation of couples' cortisol levels and mood states. *J Pers Soc Psychol* 98:92–103.
- Katz J, Beach SR, Joiner TE, Jr (1999) Contagious depression in dating couples. *J Soc Clin Psychol* 18:1–13.
- Butler EA (2015) Interpersonal affect dynamics: It takes two (and time) to tango. *Emot Rev* 7:336–341.
- Thoits PA (2010) Stress and health: Major findings and policy implications. *J Health Soc Behav* 51:S41–S53.
- Cohen S, Tyrrell DA, Smith AP (1991) Psychological stress and susceptibility to the common cold. *N Engl J Med* 325:606–612.
- Svensson T, Titilinski M, Engström G, Melander O (2017) Psychological stress and risk of incident atrial fibrillation in men and women with known atrial fibrillation genetic risk scores. *Sci Rep* 7:42613.
- Brodaty H, McGilchrist C, Harris L, Peters KE (1993) Time until institutionalization and death in patients with dementia. Role of caregiver training and risk factors. *Arch Neurol* 50:643–650.
- Levenson RW, et al. (2017) Emotion. *Handbook of Psychophysiology*, eds Cacioppo JT, Tassinary LG, Berntson GG (Cambridge Univ Press, Cambridge, UK), 4th Ed, pp 444–464.
- Neary D, et al. (1998) Frontotemporal lobar degeneration: A consensus on clinical diagnostic criteria. *Neurology* 51:1546–1554.
- Gorno-Tempini ML, et al. (2011) Classification of primary progressive aphasia and its variants. *Neurology* 76:1006–1014.
- McKhann G, et al. (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34:939–944.
- Armstrong MJ, et al. (2013) Criteria for the diagnosis of corticobasal degeneration. *Neurology* 80:496–503.
- Litvan I, et al. (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): Report of the NINDS-SPSP international workshop. *Neurology* 47:1–9.
- Leon AC, Friedman RA, Sweeney JA, Brown RP, Mann JJ (1990) Statistical issues in the identification of risk factors for suicidal behavior: The application of survival analysis. *Psychiatry Res* 31:99–108.
- Morris JC (1993) The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* 43:2412–2414.
- Cummings JL (1997) The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology* 48(Suppl 6):S10–S16.
- Ware JE, Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 30:473–483.
- Derogatis LR, Cleave PA (1977) Confirmation of the dimensional structure of the SCL-90: A study in construct validation. *J Clin Psychol* 33:981–989.
- Ware JE, Kosinski MA, Dewey JE (2000) *How to Score Version 2 of the SF-36 Health Survey* (Quality Metric, Lincoln, RI).
- Chiu WZ, et al. (2010) Survival in progressive supranuclear palsy and frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 81:441–445.

44. Hebert LE, Weuve J, Scherr PA, Evans DA (2013) Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology* 80:1778–1783.
45. Pinquart M, Sörensen S (2006) Helping caregivers of persons with dementia: Which interventions work and how large are their effects? *Int Psychogeriatr* 18:577–595.
46. Barrowclough C, et al. (2001) A randomized trial of the effectiveness of cognitive-behavioral therapy and supportive counseling for anxiety symptoms in older adults. *J Consult Clin Psychol* 69:756–762.
47. Lyketsos CG, et al. (2002) Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA* 288:1475–1483.
48. Reisberg B, et al.; Memantine Study Group (2003) Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* 348:1333–1341.
49. Andersen K, et al.; EURODEM Incidence Research Group (1999) Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. *Neurology* 53:1992–1997.
50. Wilson IB, Cleary PD (1995) Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA* 273:59–65.
51. de Jonghe F, Kool S, van Aalst G, Dekker J, Peen J (2001) Combining psychotherapy and antidepressants in the treatment of depression. *J Affect Disord* 64:217–229.