

Risk Factors of Distress in Alzheimer's Patients

Xiaolin Zhou,¹MD, MMed, Jie Xu,^{2,3}MMed, Yongbo Zhao,¹MD, MMed

Abstract:

Introduction: Distress of Alzheimer's disease (AD) contribute significantly to decreased quality of life, increased morbidity, higher levels of caregiver distress, and the decision to institutionalise a patient. However, the risk factors of distress in AD patients have not been thoroughly discussed. The aim of this study was to identify the risk factors of distress in AD patients. **Materials and Methods:** A large randomised controlled clinical trial on AD was analysed in this study. Both linear regression and decision tree models were used to identify the factors of distress in AD patients. **Results:** The following variables were recognised as risk factors for AD patient's distress: Care recipients often visit physicians or have medical examinations; Care recipients take medicines that affect the central nervous system or stomach; Care recipients seldom visit nurses; Caregivers have chronic disease or cancer; Caregiver experience distress, feel lonely, or have an unsatisfactory relationship with patients. In addition, caregiver's smoking and drinking were found to correlate negatively with AD patient's distress. **Conclusions:** Multiple factors influence the distress of Alzheimer's patients, including patient's examination and medication, patient-caregiver relationships, caregiver's psychological and physical status, and the use of nursing services. These factors should be targeted when designing prevention and intervention strategies.

Ann Acad Med Singapore 2007;36:253-8

Key words: Alzheimer's disease, Distress, Factors

Introduction

Neuropsychiatric disturbances are a major feature of Alzheimer's disease (AD) and other dementia. Behavioural abnormalities may contribute significantly to decreased quality of life, increased morbidity, higher levels of caregiver distress, and the decision to institutionalise a patient.¹⁻³ In the few studies devoted to this topic, distress is identified as an important behavioural symptom in AD and other forms of dementia, and it may be an accelerator of the disease.⁴ Knowledge of its risk factors would be very beneficial in the prevention and early intervention of distress (anxiety or depression) in AD patients.

Although a few studies have focused on the risk factors of distress in the caregivers of AD patients,⁵⁻⁷ the factors that affect the distress of AD patients have not been discussed. In this study, linear regression and decision tree models were used to identify the risk factors of distress in AD patients.

Linear regression attempts to model the relationship

between explanatory variables and a response variable by fitting a linear equation to observed data, while decision trees build up a tree of arbitrary degrees to classify instances. Each leaf-node of a decision tree represents a complete classification of a given instance, and each non-leaf node represents a variable test. These variables can directly affect the classification result and should be considered key factors. Linear regression and decision trees, as typical linear and non-linear models, were simultaneously used to recognise the risk factors of AD patient's distress.

Materials and Methods

Data Preparation

The clinical data analysed in this study were from the Resources for Enhancing Alzheimer's Caregiver Health (REACH), a multisite intervention trial for caregivers of persons with AD designed to reduce caregiver burden and depression.⁸⁻¹⁰ REACH is the largest randomised

¹ Department of Neurology, The Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai, PR China

² SWITCH Laboratory, Flanders Institute for Biotechnology (VIB), Free University of Brussels, Brussels, Belgium

³ Department of General Surgery, The Shanghai Tenth People's Hospital, Shanghai Tongji University, Shanghai, PR China

Address for Correspondence: Dr Xiaolin Zhou, Department of Neurology, Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai, PR China 200080.

Email: zhou_xiaolin@163.com

controlled clinical trial to date, involving thousands of caregiver and care recipient dyads recruited from 6 different sites in the United States. In the patient selection process, the principal investigator must verify a clinical diagnosis of AD not due to memory problems because of a severe mental illness or past head injury respectively, by reviewing diagnostic records and consulting the care recipient's primary care physician. If the investigator is unable to obtain a clear diagnosis of AD, the care recipient is ineligible for the study. The REACH database included 40 datasets, 6 of which had more than 3000 instances and were used in this study: "Care Recipient Medications", "Formal Care and Services", "Caregiver Health and Health Behaviours", "Anxiety Inventory", "Social Activities", and "Revised Memory and Behaviour Checklist" (Table 1).

All variables in these datasets were assessed during the interviews with caregivers. For example, "Revised Memory and Behaviour Checklist" represented the memory and behaviour status of care recipients. It was assessed using a series of questionnaires completed by the caregiver (e.g., Has care recipient experienced any memory or behaviour problems?), and their answers were translated into integers from 1 to 4 as: 1 = "Not at all", 2 = "Somewhat", 3 = "Moderately", 4 = "Very much". The questionnaires in the utilised datasets are shown in Appendix.

Before linear regression analysis, the 6 selected datasets were integrated into one larger dataset. As the datasets had different instance numbers, only those patients simultaneously included in 6 datasets were collected into the larger dataset. After this step, we filtered the instances that had more than 20 missing values, and the selection of variables followed these rules:

- I. Delete all marking variables, such as patient ID number and date of interview.
- II. Use all remaining variables from "Care Recipient Medications", "Formal Care and Services", "Caregiver Health and Health Behaviours", "Anxiety Inventory", "Social Activities", and "Revised Memory and Behaviour Checklist" (except ANX) as independent variables.

III. Use the variable "ANX" (indicating distress of care recipients) from the dataset "Revised Memory and Behaviour Checklist" as dependent variable (predicted variable).

The final dataset (hereinafter referred to as "dataset") comprised 3370 instances and 153 variables (including "ANX"). Most variables in the dataset had integer values ranging from 1 to 4.

The information on the characteristics of Alzheimer's patients and their caregivers are shown in Table 2. The disease stages of most patients were considerably serious, and more than 90% of the patients had problems in carrying out activities of daily living. Most caregivers spent more than 10 hours per day caring for patients. The smoking subjects consumed 3.7 cigarettes per day on average, while drinkers consumed alcohol 2.4 times per day on average.

Analysing Models

We used linear regression and decision tree models to analyse the factors that affect the levels of distress in AD patients. Linear regression estimated the coefficients of the linear equation, involving one or more independent variables that best predict the value of the dependent variable. The variable selection method was stepwise (criteria: probability of F to enter ≤ 0.050 , probability of F to remove ≥ 0.100).

In this study, the decision tree was generated by WEKA, a machine-learning software package written in Java. The number of boosting iterations was set at 10 to suit the dataset and the desired complexity-accuracy tradeoff. Induction of the trees was optimised, and heuristic search methods were introduced to speed learning.¹¹

Results

In this study, 67.2% of the total variance in ANX was explained by the linear regression model, which included 13 independent variables (Table 3). The variables in positive correlation with ANX could be grouped into 4 categories: care recipient's visit and examination (visits to physician, visited physician's assistant, and medical examinations), care recipient's medication (taking medicines for central

Table 1. Datasets Analysed in this Study

Names of the datasets	Purpose	Variables	Instances
Care Recipient Medications	Medications taken by CR	149	3389
Formal Care and Services	Community-based medical and other care services for CR	21	3389
Social Activity	Social activities of CR	16	
Revised Memory and Behaviour Checklist	Memory and behavioural problems of CR	17	3389
Caregiver Health and Health Behaviours	Physical health status and everyday health-related behaviours of the CG	16	4133
Anxiety Inventory	Anxiety of CG	14	4133

CG: caregiver; CR: care recipient

Table 2. Information on Characteristics of Alzheimer’s Patients and Their Caregivers

	Alzheimer’s patients	Caregivers
Gender: Male	43.1%	19.2%
Average age (y)	76.2	54.5
Duration of illness (y)	6.4	0
Feel anxious	44.3%	27.4%
Smoke cigarettes	13.8%	14.9%
Consume alcohol	15.1%	17.6%
Problems with food preparation	96.6%	0.4%
Problems with paying bills	96.2%	0%
Problems with travelling independently	96.0%	0%
Problems with shopping	95.8%	0%
Problems with housekeeping	91.2%	0%
Had cancer	4.4%	0.2%
Undergoing chemotherapy	0.3%	0%

nervous system), content of caregiver’s service (receive day care, meals delivered to home), caregiver’s distress (feel jittery, feel tense), and caregiver’s health status (have stomach or bowel problems, have cancer). Three variables were in negative correlation with ANX (i.e., visited nurse, smoke cigarettes now, and more than 2 drinks per day).

The resultant decision tree had 10 non-leaf nodes (Fig. 1). The paths to leaf-nodes along the decision tree can be changed into logical rules. For example, the path through nodes 1!6!10 can be translated into: If a caregiver does not feel jittery or tense but seldom have fun with other people,

the care recipient will be prone to experience distress (**rule 1**). Other paths that result in distress can be translated as following:

Nodes 1→ 4: Caregiver often feels jittery, and often visits psychiatrist (**rule 2**).

Nodes 1→ 6: Caregiver does not feel jittery, but feels tense (**rule 3**).

Nodes 2→ 8→ 9: Care recipient often visits physician and often has medical examinations (**rule 4**).

Nodes 3→ 7: Care recipient often visits physician’s assistant and takes medication for stomach ailments (**rule 5**).

Node 5: Care recipient seldom visits nurse (**rule 6**).

From these rules, the risk factors for AD patient’s distress can be summarised as following: caregiver’s loneliness (rule 1); caregiver experiencing distress (rule 2 and 3); care recipient often has medical examination (rule 4); care recipient has chronic disease (rule 5); and lack of nursing service (rule 6).

Discussion

In this study, the risk factors of distress in Alzheimer’s patients have been recognised for the first time using large dataset and multiple analysing models. The dataset comprised 3370 instances and 153 variables, describing Alzheimer’s patients and their caregivers from different cities. Both linear regression and decision tree models were used to recognise the risk factors. As a result, the 2 models reported different sets of correlated variables.

In the linear regression model, 7 main factors were

Table 3. Independent Variables in the Resultant Linear Regression Model

Variables	Label	Beta*	t	Sig
RVSP	(CR) visits to physician (times/month)	0.05499	2.93688	0.00333
RVS	(CR) visited physician’s assistant	0.05917	3.44417	0.00058
RXY	(CR) Medical examinations (times/month)	0.04970	2.65540	0.00795
CKM	(CR) meals delivered to home (times/month)	0.08414	2.32944	0.01989
SPGR	(CR) receive day care	0.03963	2.32394	0.02018
R5C2	(CR) drugs affecting central nervous system	0.04219	2.49202	0.01275
VISN	(CR) visited nurse	-0.06160	-3.59494	0.00032
JITTR	(CG) was jittery.	0.07141	3.56761	0.00036
SBPRO	(CG) have stomach or bowel problems	0.04365	2.50105	0.01243
CA	(CG) have cancer	0.03846	2.21439	0.02724
TENSE	(CG) feel tense	0.04813	2.39740	0.01656
CIGN	(CG) smoke cigarettes now	-0.03470	-2.03491	0.04193
TDRIN	(CG) more than two drinks per day	-0.03500	-3.02432	0.00353

*Beta: standardised coefficients; CR: care recipient; CG: caregivers

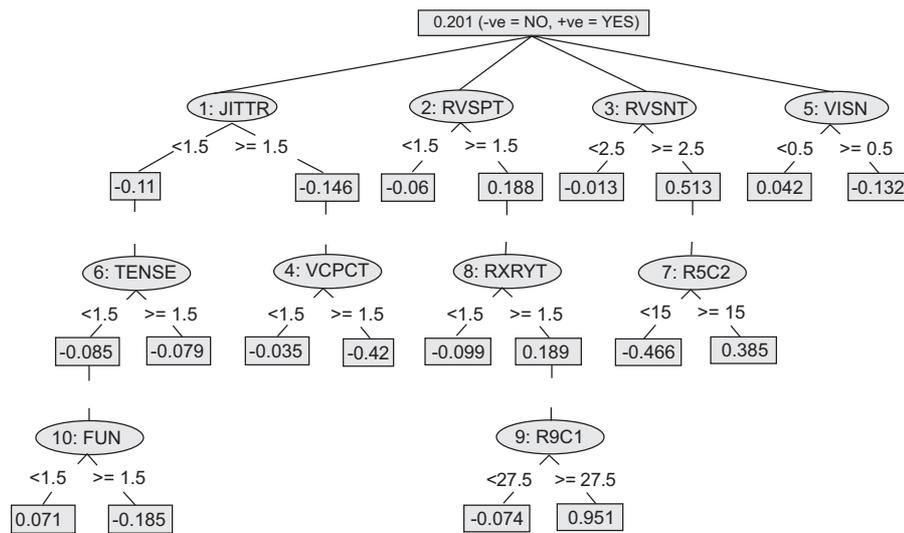


Fig. 1. The decision tree structure. The variable “VCPCT” (in node 4) indicated the times a caregiver saw a psychiatrist per month. Variable “R9C1” (node 9) indicated gastric medicines taken by care recipients, and “Fun” (node 10) meant the time for caregivers to have fun with other people. Labels for other variables can be found in Table 4.

associated with the distress of AD patients:

Care recipients often visit physicians or their assistants, and undergo more medical examinations. These conditions usually appear when a patient's disease is unstable or deteriorating. Frequent medical examinations may make patients worried about their own health condition. In order to reduce the patient's distress, it may be helpful to avoid unnecessary medical examinations.

Care recipients taking medicines that affect the central nervous system. The use of central nervous system depressants and stimulants may be either the cause or the result of the patient's distress. Due to the fact that many patients using depressants or stimulants still experience distress, the use of these medicines should be intensively monitored. The withdrawal effects of these drugs should be detected and treated early as they may also contribute to patient's distress.

Care recipients seldom visit nurses. Nursing services may play a role in reducing the distress of AD patients. A recent study also indicated that nurses could play a pivotal role in intervening with family caregivers and decreasing their depressive symptoms.¹² Although the medical condition of the patients in this study were considerably serious, only 11% of them often used nursing services. It is necessary to establish more prospective controlled trials to better understand the role of nursing in reducing the distress of AD patients.

Caregivers do not carefully serve patients, or do not prepare meals for patients. This may be a result of unsatisfactory patient-caregiver relationship. A study¹³ has

shown that poor caregiver-patient relationship is associated with distress among caregivers of AD patients. This study also indicated its correlation with patient's distress. For the sake of reducing patient's and caregiver's distress, pre-illness personal relationship should be considered when selecting caregivers, as it was found that caregivers who had a close relationship with the patient before illness onset tended to feel less burden or distress.¹⁴

Caregiver is experiencing distress. Our study indicates that the distress of an Alzheimer's patient and his or her caregiver are positively associated. Similar association has also been found between cancer patients and their caregivers.¹⁵ These findings indicate that the treatment of patient's and caregiver's distress should be planned as a whole.

Caregivers have chronic disease or cancer. In fact, distress is fairly contagious in families confronted with chronic illness, particularly in families with limited financial resources and inadequate insurance coverage.¹⁶ Thus, effective treatment strategies may need to be targeted at all members of the AD patient's family. Providers should be particularly vigilant about intra-family effects when their patients come from families that lack the financial resources that may bolster the stress of caring for a family member with a chronic illness.

Caregiver's smoking and drinking were found to correlate negatively with AD patient's distress. In this study, the percentage of caregivers consuming cigarette and alcohol were 14.9% and 17.6%, respectively. The protective effects of smoking and drinking on AD have been examined in several epidemiological studies.^{17,18} However, this is the

first time an association between the decreased distress of Alzheimer's patients and caregiver's smoking or drinking has been found. This phenomenon may be due to the tendency of certain individuals to use cigarettes or alcohol as a means of regulating anxiety and depression.^{19,20} Certain caregivers may have released their distress using cigarettes and alcohol, thus reducing the negative effect of their feelings on care recipients. As smoking and drinking are risk behaviours, it would be meaningful to increase the availability of social and treatment resources that serve as alternatives to reducing stress.

The result of decision tree analysis was partially different with linear regression. In particular, it reported stomach medicines to be correlated with the distress of AD patients, which can be explained by the strong correlation between distress and gastric ulcer. Moreover, the decision tree reported caregiver's loneliness as a risk factor of distress in AD patients. The isolation and taciturnity of caregivers may affect AD patients and make them feel anxious. On the other hand, isolation often makes the caregiver lack disease knowledge and caring experience,²¹ and problematic caring may make patients feel helpless and anxious.¹³ To support caregivers, it would be useful to establish more caregivers' schools and communities to improve their caring knowledge and experiences.

In the 2 analysing models, some variables were found to have no correlation with the distress of AD patients. Firstly, most of the medicines taken by patients (except those for central nervous system and stomach) had no correlation with distress. These included cardiovascular regulators, anti-diabetics, anti-rheumatics, anti-asthmatics, and antibiotics. Other uncorrelated patient's variables included feeling lonely, attending a day health programme for seniors, visiting emergency room, and being in a hospital overnight. Uncorrelated caregiver's variables included having medical examinations, visiting emergency room, having been a patient in a nursing home, doing vigorous exercises, and eating fewer than 2 meals per day.

Conclusion

Based on a large dataset and multiple analysis models, we have come to these conclusions: Alzheimer's patients tend to experience distress if they frequently visit physicians or undergo medical examinations. Moreover, unsatisfactory patient-caregiver relationship may be a cause of AD patient's distress. If caregivers often experience distress, feel lonely or have chronic disease or cancer, patients will be more likely to experience distress. These factors should be targeted when designing prevention and intervention strategies.

Acknowledgements

This work is sponsored by the Natural Science Foundation of Shanghai Municipality of China under Grant No. 01ZB14050. Jie Xu is supported by the Shanghai Rising Star Program, Type A, No. 06QA14041.

REFERENCES

1. Levy ML, Cummings JL, Kahn-Rose R. Neuropsychiatric symptoms and cholinergic therapy for Alzheimer's disease. *Gerontology* 1999;45(suppl 1):15-22.
2. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. *Neurology* 1996;46:130-5.
3. Russo J, Vitaliano PP, Brewer DD, Katon W, Becker J. Psychiatric disorders in spouse caregivers of care recipients with Alzheimer's disease and matched controls: a diathesis-stress model of psychopathology. *J Abnorm Psychol* 1995;104:197-204.
4. Jost BC, Grossberg GT. The evolution of psychiatric symptoms in Alzheimer's disease: a natural history study. *J Am Geriatr Soc* 1996; 44:1078-81.
5. Rinaldi P, Spazzafumo L, Mastriforti R, Mattioli P, Marvardi M, Polidori MC, et al; Study Group on Brain Aging of the Italian Society of Gerontology and Geriatrics. Predictors of high level of burden and distress in caregivers of demented patients: results of an Italian multicenter study. *Int J Geriatr Psychiatry* 2005;20:168-74.
6. Aguglia E, Onor ML, Trevisiol M, Negro C, Saina M, Maso E. Stress in the caregivers of Alzheimer's patients: an experimental investigation in Italy. *Am J Alzheimers Dis Other Demen* 2004;19:248-52.
7. Covinsky KE, Newcomer R, Fox P, Wood J, Sands L, Dane K, et al. Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. *J Gen Intern Med* 2003;18: 1006-14.
8. Schulz R, Burgio L, Burns R, Eisdorfer C, Gallagher-Thompson D, Gitlin LN, et al. Resources for Enhancing Alzheimer's Caregiver Health (REACH): overview, site-specific outcomes, and future directions. *Gerontologist* 2003;43:514-20.
9. Wisniewski SR, Belle SH, Coon DW, Marcus SM, Ory MG, Burgio LD, et al. The Resources for Enhancing Alzheimer's Caregiver Health (REACH): project design and baseline characteristics. *Psychol Aging* 2003;18:375-84.
10. Schulz R, Belle SH, Czaja SJ, Gitlin LN, Wisniewski SR, Ory MG; REACH Investigators. Introduction to the special section on Resources for Enhancing Alzheimer's Caregiver Health (REACH). *Psychol Aging* 2003;18:357-60.
11. Rumelhart DE, Hinton GE, Williams RJ. Learning internal representations by error propagation. In: Rumelhart DE, editor. *Parallel Distributed Processing: Explorations in the Microstructure of Cognition*. Cambridge, MA: MIT Press, 1986:45-76.
12. Farran CJ, Loukissa DA, Lindeman DA, McCann JJ, Bienias JL. Caring for self while caring for others: the two-track life of coping with Alzheimer's disease. *J Gerontol Nurs* 2004;30:38-46.
13. Beeson R, Horton-Deutsch S, Farran C, et al. Loneliness and depression in caregivers of persons with Alzheimer's disease or related disorders. *Issues Ment Health Nurs* 2000;21:779-806.
14. Williamson GM, Schulz R. Relationship orientation, quality of prior relationship, and distress among caregivers of Alzheimer's patients. *Psychol Aging* 1990;5:502-9.
15. Hodges LJ, Humphris GM, Macfarlane G. A meta-analytic investigation of the relationship between the psychological distress of cancer patients

- and their carers. *Soc Sci Med* 2005;60:1-12.
16. Holmes AM, Deb P. The effect of chronic illness on the psychological health of family members. *J Ment Health Policy Econ* 2003;6:13-22.
 17. Lee PN. Smoking and Alzheimer's disease: a review of the epidemiological evidence. *Neuroepidemiology* 1994;13:131-44.
 18. Letenneur L, Larrieu S, Barberger-Gateau P. Alcohol and tobacco consumption as risk factors of dementia: a review of epidemiological studies. *Biomed Pharmacother* 2004;58:95-9.
 19. Honda K. Psychosocial correlates of smoking cessation among elderly ever-smokers in the United States. *Addict Behav* 2005;30:375-81.
 20. Hill TD, Angel RJ. Neighborhood disorder, psychological distress, and heavy drinking. *Soc Sci Med* 2005;61:965-75.
 21. Gruffydd E, Randle J. Alzheimer's disease and the psychosocial burden for caregivers. *Community Pract* 2006;79:15-8.

Appendix. Corresponding questionnaires for datasets "Revised Memory and Behaviour Checklist", "Formal Care and Services", and "Caregiver Health and Health Behaviours"

Revised Memory and Behaviour Checklist

- Has CR experienced any memory or behaviour problems?
 Has CR been asking the same question over and over?
 Has CR had trouble remembering recent events (e.g., items in the newspaper or on television)?
 Has CR had trouble remembering significant past events?
 Has CR been losing or misplacing things?
 Has CR been forgetting what day it is?
 Has CR been starting but not finishing things?
 Has CR had difficulty concentrating on a task?
 Has CR been doing things that embarrass you?
 Has CR been waking you or other family members up at night?
 Has CR been talking loudly and rapidly?

Has CR appeared anxious or depressed? (ANX, the dependent variable)

- Has CR been talking about feeling lonely?
 Has CR made comments about feeling worthless or being a burden to others?
 Has CR made comments about feeling like a failure or about not having any worthwhile accomplishments in life?
 Has CR been arguing, irritable, and/or complaining?
 Has CR had any other memory or behaviour problems that I haven't already mentioned?

Formal Care and Services

- Do you or (CR) have a homemaker who helps with shopping, cleaning, laundry, preparing meals, etc.?
 Do you or (CR) have a home health aid come to the home to help with personal care (i.e., bathing, feeding and health care tasks)?
 Do you or (CR) have cooked meals delivered to home or go to a centre for low-cost meals?
 Do you or (CR) have a formal service that provides transportation to places outside the home (i.e., doctors, clinics and shopping)?
 Do you or (CR) have a visiting nurse come to check medications, blood pressure or other medical needs?
 Do you or (CR) attend a senior day care or senior day health programme?

- Are you (CG only) attending any support groups on a regular basis?
 Have you (CG only) had any visits to a physician?
 Has (CR) had any visits to a physician?
 Have you (CG only) had any visits to a nurse, physician's assistant or non-physician practitioner?
 Has (CR) had any visits to a nurse, physician's assistant or non-physician practitioner?
 Do you or (CR) see a counselor, psychiatrist, psychologist or clergy for help with personal or family problems?
 Have you (CG only) had any visits to an emergency room?
 Has (CR) had any visits to an emergency room?
 Have you (CG only) had any X-rays, blood tests, urine tests, MRIs or CAT scans?
 Has (CR) had any X-rays, blood tests, urine tests, MRIs or CAT scans?
 Have you (CG only) been a patient in a hospital overnight or admitted as a patient to a hospital and discharged on the same day?
 Has (CR) been a patient in a hospital overnight or admitted as a patient to a hospital and discharged on the same day?
 Have you (CG only) been a patient in a nursing home?
 Has (CR) been a patient in a nursing home?
 Do you or (CR) receive any other service from an agency or organisation?

Caregiver Health and Health Behaviours

- Is your general health status very good?
 Do you currently have, or has a doctor told you that you have, any of the following health problems? (Arthritis, high blood pressure, heart condition, chronic lung disease such as chronic bronchitis or emphysema, diabetes, cancer and stroke)
 During the past 2 weeks, to what extent have you experienced the following symptoms: (Dizziness, headaches, and stomach or bowel problems?)
 Do you typically eat fewer than 2 meals per day?
 Do you have 2 or more drinks of beer, liquor or wine almost every day?
 Do you do vigorous exercises for 15 to 30 minutes or more at least 3 times a week?
 Do you smoke cigarettes now?

CG: caregiver; CR: care recipient; MRI: magnetic resonance imaging