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Increased Risk of Dementia When Spouse Has Dementia? The Cache County Study

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Abstract

Objectives—Chronic psychosocial stress in caregivers can lead to adverse health outcomes including depression, anxiety, and cognitive decline. We examined the effects of having a spouse with dementia on one's own risk for incident dementia.

Design—Population-based study of incident dementia in spouses of persons with dementia.

Setting—Rural county in northern Utah.

Participants—2,442 subjects (1,221 married couples) aged 65 and older.

Measurements—Incident dementia was diagnosed in 255 subjects, with onset defined as age when subject met DSM-III-R criteria for dementia. Cox proportional hazards regression tested the effect of time-dependent exposure to dementia in one's spouse, adjusted for potential confounders.

Results—A subject whose spouse experienced incident dementia onset had a six-fold increase in the hazard for incident dementia compared to subjects whose spouses were dementia free [Hazard Rate Ratio (HRR)=6.0, 95% CI: 2.2–16.2 ($p<.001$)]. In sex-specific analyses, husbands had higher risks (HRR=11.9, 95% CI: 1.7–85.5, $p=.014$) compared to wives (HRR=3.7, 95% CI: 1.2–11.6, $p=.028$).

Conclusion—The chronic and often severe stress associated with dementia caregiving may exert substantial risk for the development of dementia in spouse caregivers. Additional (not mutually exclusive) explanations for findings are discussed.

Keywords

dementia; caregiving; stress

INTRODUCTION

Informal (unpaid) dementia caregiving for a spouse is a natural marital obligation, and spousal caregivers may report positive feelings toward caregiving. ¹ Yet, dementia caregiving is difficult, requiring time, energy and usually physical exertion in provision of personal and instrumental assistance to a spouse with dementia (the care recipient). Dementia caregiving can incur a sense of loss of personal control or individual being, ² and is also associated with depression ^{3–4}, physical health problems ⁵ and mortality. ⁶ Dementia caregivers have been shown to provide more assistance, and to report more personal sacrifices and stress, than those who care for physically-impaired elderly. ⁷

Generally, spouses of persons who suffer from dementia experience considerable stress, observing the deterioration of their life partner. The effects of this stress, which have been most studied in the context of caregiving, may increase the risk of negative cognitive outcomes in the spouse although this has been relatively unexplored. One possible mechanism is the detrimental effects of chronic stress on the hippocampus, a brain region responsible for memory. ^{8–10} There may be a relationship between having a spouse with dementia and adverse cognitive function with stress as potential mediator. Caswell et al showed that lower scores on a digit-symbol test of complex attention and cognitive speed in

caregivers of spouses with dementia (compared to non-caregiving controls) were no longer significant after control for subjective stress. 11 This suggests that distress explains the link between exposures and adverse cognitive outcomes in spouses of persons with dementia. The Nurses Health Study showed that female caregivers of ill spouses performed worse than others on a general cognitive screening test. 12 One longitudinal study found decline in vocabulary over a two-year period was greater in caregivers of spouses with dementia than in controls. 13 Higher hostile attribution and metabolic risk in caregivers mediated the decline, again implicating stress as a potential mechanism. deVugt et al 14 found that spouse dementia caregivers had significantly worse general cognitive functioning compared to controls. Mackenzie et al 15 demonstrated that caregivers of relatives in palliative care exhibited significant cognitive impairment, compared to a control sample. After death of care recipient, there was further deterioration on episodic and working memory but improvement in attentional resources, suggesting “.... the possibility of reversing certain cognitive deficits by reducing caregiver stress.” (p. 750). Finally, Vitaliano et al 16 recently reported that spouse dementia caregivers scored lower on a digit symbol test than non-caregiving controls at baseline, and declined 4.5 times faster than non-caregivers over two years. Greater depressed mood in caregivers mediated this association, further implicating distress associated with spousal dementia caregiving as a possible causal explanation for declining cognitive function in the caregiver.

These studies were unfortunately limited by small sample size. Only a few were longitudinal (limiting causal attribution) and none included a detailed clinical assessment for dementia.

We report here results from a population-based study of dementia in which 2,442 older married individuals participated for up to 12 years of longitudinal cognitive evaluation. We used a careful dementia ascertainment protocol to diagnose dementia in both spouses. Age of dementia onset was determined for each spouse, facilitating time-dependent analyses of the effect of having a spouse with dementia. We hypothesized that older married adults would be at increased risk for incident dementia, after onset of dementia in one's spouse. Given that female caregivers are significantly more likely to report poor well-being, 17 depression, and anxiety 18 than male caregivers, we explored whether the effect of having a spouse with dementia would be greater for women than men.

METHODS

The current report uses extant data from the Cache County (Utah) Study (CCS) on Memory Health and Aging. Study procedures were approved by the Institutional Review Boards of Utah State University, Duke University, and The Johns Hopkins University. Informed consent was obtained from study participants at each stage of the study.

Participants

The CCS is a population-based epidemiological study of dementia. In 1995 we invited all 5,756 elderly (age 65 years or older) permanent residents of the county to join the study. 5,092 (90%) agreed to a baseline interview. 3,299 were married, 1,534 widowed, 167 divorced or separated, 82 had never married, and 10 had unknown marital status. Among married respondents, 2,738 (83%) had a spouse who was also a CCS participant. The present work focuses only on married couples where both spouses were CCS baseline participants.

During baseline procedures, 296 subjects were identified as having dementia. These individuals were excluded and the remaining analysis sample comprised 2,442 participants from 1,221 married couples. Incident dementia was diagnosed over three triennial waves as follows: diagnosis only in the husband (n=125), only in the wife (n=70), in both spouses (n=30), in neither (n=996). In only 10 couples (0.4%) one spouse resided in a nursing home

at baseline; further, institutionalization after dementia onset occurred in only 12% of incident cases; all others were co-resident over the entire period of observation. Participants “exposed” to a spouse with dementia were observed an average of 9.2 (SD 3.1) years, including 5.1 (SD 3.2) years before and 4.1 (SD 3.2) years after their spouse’s dementia onset. Unexposed participants were followed slightly longer (mean 4.5, SD 4.2 years).

Dementia Ascertainment

Dementia was diagnosed using an identical protocol for all participants. However, spouses of persons with dementia were not explicitly identified as “caregivers,” nor were data collected on actual caregiver activities or stress. Thus, the exposure investigated herein is “having a spouse with dementia,” and not spousal dementia caregiving, per se, although in most instances, coresident spouses likely filled a substantial caregiving role.

Clinical Evaluation

The CCS utilized a multi-stage dementia ascertainment protocol repeated in four waves (1995–7, 1998–2000, 2002–4, and 2005–7). 19 Briefly, screening began with an in-person interview including the modified Mini-Mental State examination (3MS) 20 or, for those unable to participate, the Informant Questionnaire for Cognitive Disorder in the Elderly (IQCODE). 21 Participants whose screening scores suggested possible dementia then completed an in-depth clinical assessment (CA), as did a 19% designated sub-sample. Specially trained nurses and psychometric technicians administered the CA, which included a brief physical evaluation, a history of medical and cognitive symptoms, a structured neurological examination, and a one-hour battery of neuropsychological tests.

A geriatric psychiatrist and neuropsychologist, along with the assessment team, reviewed these data and assigned working DSM-III-R diagnoses of dementia or other cognitive syndromes. Subjects with a working diagnosis of dementia were selected for geriatric psychiatric examinations and laboratory studies. To substantiate or refine their diagnoses, these individuals were re-examined 18 months after their initial CA. A multidisciplinary consensus panel of dementia experts reviewed all available data and assigned final consensus diagnoses. Onset was defined as the year in which a participant unambiguously met DSM-III-R criteria for dementia.

Imputation of Incident Dementia for Subjects with Incomplete Ascertainment

In the final sample of 2,442 participants, there were 253 subjects who screened positive for dementia but failed to complete the CA (owing to death, refusal or moving out of area between screening and CA). We dealt with this missing data problem by imputing dementia status, based on their last screening test performance, employing conservative diagnostic criteria for dementia, as follows. In Waves 1 and 2, individuals who screened positive on the 3MS or IQCODE were asked to undergo evaluation with the Dementia Questionnaire (DQ) prior to being assigned to undergo a CA. 22 DQ interviews were rated as 1=cognitively normal, 2=mild, 3=moderate, 4=severe cognitive impairment, or 5=dementia.

When DQ results were available, we relied on these scores in preference to other methods of imputing dementia status for subjects lacking a CA, assuming that dementia was present in subjects with a DQ rating of 5 and was absent in others. When no DQ was available, screening data were used: if the IQCODE score was ≥ 3.6 (Sensitivity =.80, and Sensitivity =.82) 21 or if the 3MS was below an age/gender/education-specific cut-off score, 20 dementia was imputed, and non-dementia was imputed otherwise. Subjects with imputed dementia were assumed to have experienced dementia onset mid-way between the point at which DQ or screening data were used for imputation, and the prior wave with normal cognitive status. In combination, these strategies enabled us to consider 1,092 person-years

of observation that would otherwise have been ignored. Of the 255 subjects with incident dementia, 203 (80%) were diagnosed clinically and the remaining by imputation.

Covariates

Analyses considered participants' gender and age (in years) at baseline. Additionally, our models adjusted for *APOE* genotypes obtained at baseline.

To at least partially control for shared environmental exposures that might influence risk for dementia in both spouses, we adjusted for socioeconomic status (SES), a significant predictor of many health-related outcomes including dementia. Couple-level socioeconomic status SES was measured using the husband's education and occupation. Occupation of longest duration was coded into nominal categories of (1) professional, technical, managerial; (2) clerical and sales; (3) service; (4) agricultural; (5) machine/miscellaneous. The statistical dependence between spouses within a couple was also addressed via random effects modeling, as described below.

Data Analysis

We estimated a series of Cox proportional hazards regression models to examine the association between having a spouse with dementia, a time-varying covariate, and subsequent risk for incident dementia. Both crude and multivariable-adjusted models were estimated. Each subject was identified as having developed incident dementia (with age of onset to the nearest year), or was "right censored" at the last completed visit. Cox models were stratified by baseline age group (<75, 75–85, 85+ years), thus, the parameter estimate for "age" in the models reflects the general effect of each additional year of age *within* each age stratum. 24

Observation Time

To model time to incident dementia, each participant's observation time started at baseline screening and ended at 1) year of dementia onset, 2) right-censoring, or 3) the spouse's right-censoring (death or loss to follow-up), whichever took place first. When the spouse's right-censoring event occurred first, we opted to end the index subject's observation at this time, which was a conservative approach to deal with the unknown exposure thenceforward.

Exposure Time

We dated onset of exposure to having a spouse with dementia at the point of the spouse's dementia onset. Because of recent evidence showing that caregivers' neuropsychological deficits can extend beyond the death of the demented care recipient, 15 we used an approach of "once exposed, always exposed," i.e., the exposure variable was not "reset" to "no exposure" after death of the care recipient.

Adjustments for Widowhood and Dependent Observations within Dyads

Because very few unexposed subjects (0 men, 4 women) were widowed over the entire period of observations, we could not adjust for potential confounding effects of widowhood. We were concerned, however, that the risks of dementia in the second-affected spouse might reflect exposures shared by the couple rather than an effect of caregiving for dementia or the other covariates included in adjusted Cox models. To probe the possibility of another, unknown or unmeasured confounder, we fit Cox proportional hazard models that allowed for random effects. In this application, random effects represent the influence of shared unmeasured factors (but present nonetheless) that affect the hazard rate for dementia for both spouses in a couple. 24 Models that include random effects directly address the problem of statistical dependence among members of the same couple while simultaneously

controlling for unmeasured shared couple-level factors. This approach therefore correctly estimates the standard errors for the Cox regression coefficients while also reducing possible biases that would have arisen without the adjustment for the shared exposures. Models that include the random effects generated results (not shown) that were comparable to those reported here. Additionally, separate models were fit by gender, to allow individual examination of the effects of having a husband with dementia vs. a wife.

RESULTS

Husbands' baseline ages averaged 75.7 (SD 5.9) years, while wives' age averaged 73.1 (SD 5.3) years. Prior duration of marriage at baseline averaged 48.9 (SD 11.5) years, with only 40 (3.8%) of couples married for less than 10 years, and only 56 (5%) married for less than 20 years. Only four couples divorced after their baseline interview. Subjects were followed for up to 12.6 years; median follow-up was 3.3 years. Table 1 provides sample characteristics along with tests of bivariate relationships. As expected, incident dementia was significantly associated with older age and presence of one or more $\epsilon 4$ alleles at *APOE*, and having a spouse with dementia.

An unadjusted proportional hazards regression model of survival time to incident dementia revealed a substantially increased hazard for dementia after spouse's dementia onset, with Hazard Rate Ratio (HRR) = 6.4 (95% confidence interval {CI} 2.4–17.2, $p < .001$). In the fully-adjusted model (Table 2), older age, presence of at least one *APOE* $\epsilon 4$ allele (in relation to no $\epsilon 4$ allele) were all associated with higher risk of incident dementia, while higher SES (husband with professional/technical/managerial occupation) was associated with reduced risk. Although several of these covariates were strongly related to dementia outcome, the fully adjusted proportional hazards model showed a nearly identical hazard ratio for exposure to dementia in one's spouse (HRR = 6.0, CI 2.2–16.2, $p < .001$). (Note: when models were repeated without imputation for dementia among participants with incomplete ascertainment, the effect of having a spouse with dementia was comparable: HRR 7.7, CI 1.9–31.3, $p = .004$).

In analyses stratified by gender, the effect of exposure to dementia in one's spouse was higher for men (HRR = 11.9, CI = 1.7–85.5) than women (HRR = 3.7, CI = 1.2–11.6) (Table 2). Additional models (not shown) adjusted for length of marriage at baseline and its interaction with exposure to having a spouse with dementia (interaction was non-significant), with negligible impact on effect of this exposure, for both husbands and wives.

DISCUSSION

To our knowledge, this is the first population-based sample used to study risk for incident dementia among married older adults, as a function of whether spouse develops incident dementia. The finding of a six-fold increase in dementia risk, among persons so exposed, compared with married men and women whose spouse had not developed dementia, remained after adjustment for age, gender, education, SES, and *APOE* genotype, all of which were (as expected) associated with dementia risk. Length of marriage did not modify this association. Our stratified analyses suggest a more deleterious effect on husbands than on wives but, given the overlap in confidence intervals, the difference could be due to chance and needs further study.

The distress of watching one's spouse suffer from dementia, and the physical and mental burden of providing dementia care, are potential causal factors, given the influence of caregiving on elevated risk for depression 25 and mortality 6. Having a loved one with dementia is stressful regardless of age, but the burden for spouses may be even greater due

to close emotional ties to their partner, their own medical co-morbidity, greater risk for functional limitations, and greater likelihood of fatigue at physical exertion. Neuropsychiatric disturbances that are common over the course of dementia are particularly stressful and are the most common reason for institutionalization. 26 Anticipatory grief (related to loss of pre-dementia relationship as dementia progresses with spouse's impending death) has been independently associated with caregiver burden among dementia caregivers, beyond effects of caregiver characteristics and behavior problems in the care recipients. 27

It is important to note that this finding may be due to several alternative mechanisms. In the absence of direct measures of subjective stress and caregiving activities, part of the observed effect may be due to shared environmental exposures. Our models adjusted for socioeconomic status, providing at least partial adjustment for an environment conducive to healthier lifestyles shared by both spouses. Nevertheless, adjustment for SES does not provide a complete control for potential confounders, such as access to medical care, smoking, alcohol consumption and diet. However, our random effects models controlled for shared unmeasured exposures without any appreciable change in the findings. A third mechanism may be homogamy, or positive assortative mating, to the extent that shared risk for dementia in couples may be influenced by similarity in proneness to distress or mental illness 28. Thus, while the overall risk for dementia among married individuals whose spouse has dementia was high, these mechanisms are not mutually exclusive. The relative contribution of each of these potential mechanisms to this overall effect is unknown and needs further study.

The data also show that many exposed spouses are not affected. An important focus for future studies should be to better understand the strategies and contexts that limit the adverse effects of the exposure. Results of such analyses would then guide possible interventions. Study strengths include a large community-based sample that avoids the selection bias of clinical samples, 29 and availability of APOE genotypes. Its high baseline participation rate (90%) reduced concerns about non-responder bias. 30 Additional strengths are the longitudinal follow-up allowing identification of incident cases, using an in-depth clinical assessment protocol to evaluate both spouses for dementia, over four triennial waves.

CONCLUSIONS

Our results are consistent with other studies demonstrating cognitive deficits in spouses of persons with dementia 11–15 and extend the findings to include incident dementia risk. We found a clear increased risk of incident dementia among older adults whose spouses have dementia. However, further study is needed to isolate specific mechanisms, thus identifying particular vulnerabilities among spouses so exposed. If caregiver stress is more definitively found to play a causal role, subsequent studies may examine the effect of the spouse's rate of clinical dementia progression and behavioral disturbances, to identify specific patterns that are more stressful to spouses of persons with dementia. Such information could be used to develop interventions for more vulnerable individuals. If shared environmental factors play a major role, it will likewise be important to identify key factors in the environment that are amenable to intervention. Regardless of whether one or multiple mechanisms are operating to bring about this overall effect, it is imperative that more research be conducted to help protect older adults with spouses who are suffering from dementia, from suffering the same fate themselves.

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References

1. Bacon E, Milne DL, Sheikh AI, et al. Positive experiences in caregivers: an exploratory case series. *Behav Cogn Psychother*. 2009 Jan; 37(1):95–114. [PubMed: 19364411]
2. Boss P, Caron W, Horbal J, et al. Predictors of depression in caregivers of dementia patients: Boundary ambiguity and mastery. *Family Processes*. 1990; 29:245–254.
3. Pinquart M, Sörensen S. Differences between caregivers and noncaregivers in psychological health and physical health: A meta-analysis. *Psychol Aging*. 2003; 18:250–267. [PubMed: 12825775]
4. Sörensen S, Duberstein P, Gill D, et al. Dementia care: mental health effects, intervention strategies, and clinical implications. *Lancet Neurol*. 2006 Nov; 5(11):961–73. [PubMed: 17052663]
5. Vitaliano PP, Zhang J, Scanlan JM. Is caregiving hazardous to one's physical health? A meta-analysis. *Psychol Bull*. 2003; 129:946–972. [PubMed: 14599289]
6. Schulz R, Beach S. Caregiving as a risk factor for mortality: The Caregiver Health Effects Study. *JAMA*. 1999; 282:2215–2219. [PubMed: 10605972]
7. Ory MG, Hoffman RR, Yee JL, et al. Prevalence and impact of caregiving: a detailed comparison between dementia and non-dementia caregivers. *The Gerontologist*. 1999; 39:177–185. [PubMed: 10224714]
8. Bremner JD. Does stress damage the brain? *Biol Psychiatry*. 1999; 45:979–805. [PubMed: 10386180]
9. Lupien SJ, Fiocco A, Wan N, et al. Stress hormones and human memory function across the lifespan. *Psychoneuroendocrinology*. 2005; 30:225–4. [PubMed: 15511597]
10. Lovallo, WR. *Stress and health: Biological and psychological interactions*. 2. Sage; Thousand Oaks: 2005.
11. Caswell LW, Vitaliano PP, Croyle KL, et al. Negative associations of chronic stress and cognitive performance in older adult spouse caregivers. *Exp Aging Res*. 2003; 29:303–318. [PubMed: 12775440]
12. Lee S, Kawachi I, Grodstein F. Does caregiving stress affect cognitive function in older women? *J Nervous Mental Disorders*. 2004; 192:51–57.
13. Vitaliano PP, Echeverria D, Yi J, et al. Psychophysiological mediators of caregiver stress and differential cognitive decline. *Psychol Aging*. 2005; 20:402–11. [PubMed: 16248700]
14. de Vugt ME, Jolles J, van Osch L, et al. Cognitive functioning in spousal caregivers of dementia patients: findings from the prospective MAASBED study. *Age Ageing*. 2006; 35(2):160–6. [PubMed: 16495293]
15. Mackenzie CS, Smith MC, Hasher L, et al. Cognitive functioning under stress: evidence from informal caregivers of palliative patients. *J Palliat Med*. 2007 Jun; 10(3):749–58. [PubMed: 17592987]
16. Vitaliano PP, Zhang J, Young HM, Caswell LW, Scanlan JM, Echeverria D. Depressed Mood Mediates Decline in Cognitive Processing Speed in Caregivers. *The Gerontologist*. 2009; 49(1): 12–22. 10.1093/geront/gnp004 [PubMed: 19363000]
17. Croog SH, Sudilovsky A, Burleson JA, et al. Vulnerability of husband and wife caregivers of Alzheimer disease patients to caregiving stressors. *Alzheimer's Disease and Associated Disorders*. 2001 Oct-Dec; 15(4):201–10.
18. Hooker K, Manoogian-O'Dell M, Monahan DJ, Frazier LD, Shifren K. Does type of disease matter? Gender differences among Alzheimer's and Parkinson's disease spouse caregivers. *The Gerontologist* [Gerontologist]. 2000 Oct; 40(5):568–73.
19. Breitner JC, Wyse BW, Anthony JC, et al. APOE-epsilon4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. *Neurology*. 1999; 53(2):321–331. [PubMed: 10430421]

20. Tschanz JT, Welsh-Bohmer KA, Plassman BL, et al. An adaptation of the modified mini-mental state examination: analysis of demographic influences and normative data: The Cache County Study. *Neuropsychiatry Neuropsychology and Behavioral Neurology*. 2002; 15(1):28–38.
21. Jorm AF. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): a review. *Int Psychogeriatr*. 2004; 16:275–293. [PubMed: 15559753]
22. Kawas C, Segal J, Stewart W, et al. A validation study of the dementia questionnaire. *Arch Neurol*. 1994; 51:901–906. [PubMed: 8080390]
23. Fotenos AF, Mintun MA, Snyder AZ, et al. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. *Arch Neurol*. 2008 Jan; 65(1):113–20. [PubMed: 18195148]
24. Cleves, M.; Gould, WW.; Gutierrez, RG., et al. *An Introduction to Survival Analysis Using Stata*. 2. Stata Press; 2008.
25. Covinsky KE, Newcomer R, Fox P, Wood J, Sands L, Dane K, Yaffe K. Patient and caregiver characteristics associated with depression in caregivers of patients with *dementia*. *Journal Of General Internal Medicine [J Gen Intern Med]*. 2003 Dec; 18(12):1006–14.
26. Kalapatapu RK, Neugroschl JA. Update on neuropsychiatric symptoms of dementia: evaluation and management. *Geriatrics*. 2009 Apr; 64(4):20–6. [PubMed: 19400596]
27. Holley CK, Mast BT. The impact of anticipatory grief on caregiver burden in dementia caregivers. *The Gerontologist*. 2009; 49:388–396. [PubMed: 19386826]
28. Maes HH, Neale MC, Kendler KS, Hewitt JK, Silberg JL, Foley DL, Meyer JM, Rutter M, Simonoff E, Pickles A, Eaves LJ. Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychological Medicine [Psychol Med]*. 1998 Nov; 28(6):1389–401.
29. Ramsdell J, Jackson JE, Guy HJ, et al. Comparison of clinic-based home assessment to a home visit in demented elderly patients. *Alzheimer Disease & Associated Disorders*. 2004 July/Sept; 18(3):145–153. [PubMed: 15494620]
30. Norton MC, Breitner JC, Welsh KA, et al. Characteristics of nonresponders in a community survey of the elderly. *J Am Geriatr Soc*. 1994; 42:1252–1256. [PubMed: 7983287]

Table 1

Bivariate relationships between key independent variables and incident dementia

Predictor Variable	N (%) who develop incident dementia	Bivariate tests: (t-test for continuous; chi-square test for categorical)
Having a spouse with dementia:		p=.030
Exposed (n=229)	34 (14.8 %)	
Non-exposed (n=2213)	221 (10.0%)	
Subject APOE:		p < .001
zero $\epsilon 4$ alleles (n=1629)	147 (9.0%)	
one $\epsilon 4$ allele (n=710)	85 (12.0%)	
two $\epsilon 4$ alleles (n=65)	22 (33.8%)	
Husband Occupation: *		p=.703
Professional, tech., mgt (n=1038)	100 (9.6%)	
Clerical, sales (n=198)	20 (10.1%)	
Service (n=70)	†	
Agriculture (n=518)	61 (11.8%)	
Machine/miscellaneous (n=618)	65 (10.5%)	
	n=255 incident dementia	
	n=2187 no dementia	
Subject's Age at baseline	75.9 (5.8) incident dementia	p < .001
mean ($\pm$ SD)	74.2 (5.8) no dementia	
Spouse's Age at baseline	74.7 (6.2) incident dementia	p = .402
mean ($\pm$ SD)	74.4 (5.7) no dementia	
Husband's education, years *	13.8 (3.3) incident dementia	p = .508
mean ($\pm$ SD)	14.0 (3.4) no dementia	

* Husband's education (and occupation) refers to subject's own, if male, and spouse's, if female

† Number and frequency suppressed to comply with privacy policy of Center for Medicare and Medicaid Services

Table 2

Relative hazard (95% confidence interval) of incident dementia among 2,442 married older adults as a function of whether spouse has dementia, adjusted for covariates: total sample, and stratified by spouse gender.

Predictor Variables	Total Sample	Husband as Index Subject	Wife as Index Subject
Having Spouse with Dementia	6.01 (2.23–16.17)	11.93 (1.67–85.52)	3.66 (1.15–11.61)
Female gender	0.80 (.61–1.03)	-----	-----
Age at baseline interview	1.06 (1.01–1.12)	1.02 (.98–1.07)	1.15 (1.06–1.24)
APOE Genotype*: one ε4 allele	1.45 (1.11–1.90)	1.42 (1.00–2.02)	1.55 (1.01–2.38)
APOE Genotype: two ε4 alleles	4.54 (2.86–7.23)	4.91 (2.74–8.79)	3.83 (1.68–8.72)
Husband's Occupation †: Professional, Technical, Management	0.64 (.44–.93)	.67 (.41–1.09)	.56 (.30–1.04)
Husband's Occupation: Clerical, Sales	0.66 (.40–1.10)	.57 (.28–1.15)	.79 (.38–1.66)
Husband's Occupation: Service	0.98 (.48–2.01)	1.01 (.41–2.50)	.67 (.19–2.31)
Husband's Occupation: Agriculture	0.81 (.57–1.15)	.93 (.60–1.46)	.59 (.33–1.06)
Husband's education (years)	1.00 (.95–1.05)	1.00 (.94–1.06)	1.00 (.93–1.08)

* Reference category for APOE genotype was zero ε4 alleles

† Reference category for husband's occupation was "Machine/miscellaneous"