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

[See editorial comments by Dr. Peter P. Vitaliano, pp 976–978]

Maria C. Norton, PhD,abc Ken R. Smith, PhDde Truls Østbye, MD, PhDgab JoAnn T. Tschanz, PhDbc Chris Corcoran, ScD,ci Sarah Schwartz, MS,ci Kathleen W. Piercy, PhDabc Peter V. Rabins, MD, MPHj David C. Steffens, MDkl Ingmar Skoog, MD, PhDlm John C. S. Breitner, MD, MPH,mm Kathleen A. Welsh-Bohmer, PhDm, for the Cache County Investigators

OBJECTIVES: To examine the effects of caring for a spouse with dementia on the caregiver’s risk for incident dementia.


SETTING: Rural county in northern Utah.

PARTICIPANTS: Two thousand four hundred forty-two 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 Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, 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 times greater risk for incident dementia as subjects whose spouses were dementia free (hazard rate ratio (HRR) = 6.0, 95% confidence interval (CI) = 2.2–16.2, \( P < .001 \)). In sex-specific analyses, husbands had higher risks (HRR = 11.9, 95% CI = 1.7–85.5, \( P = .01 \)) than wives (HRR = 3.7, 95% CI = 1.2–11.6, \( P = .03 \)).

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.

Key words: dementia; caregiving; stress

Informal (unpaid) dementia caregiving for a spouse is a natural marital obligation. 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 being2 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 older adults.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. One study showed that lower

From the aDepartment of Family, Consumer, and Human Development; bDepartment of Psychology; cCenter for Epidemiologic Studies; dDepartment of Family and Consumer Studies; eHuntsman Cancer Institute, University of Utah, Salt Lake City, Utah; fDepartment of Community and Family Medicine; gJoseph and Kathleen Bryan Alzheimer’s Disease Research Center, Duke University Medical Center, Durham, North Carolina; hDuke–NUS Graduate Medical School, Singapore; iDepartment of Mathematics and Statistics, Utah State University, Logan, Utah; jDepartment of Psychiatry and Behavioral Sciences, School of Medicine, Johns Hopkins University, Baltimore, Maryland; kDepartment of Psychiatry and Behavioral Sciences; lInstitute of Neuroscience and Physiology, Section of Psychiatry and Neurochemistry, Unit of Neuropsychiatric Epidemiology, University of Gothenburg, Gothenburg, Sweden; mVeterans Affairs Puget Sound Health Care System, Seattle, Washington; and nDepartment of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, Washington.

Portions of this paper were presented at the International Conference on Alzheimer's Disease in Vienna, Austria, July 11–16, 2009.

Address correspondence to Maria Norton, Cache County Memory Study, Utah State University, 4440 Old Main Hill, Logan, UT 84322. E-mail: maria.norton@usu.edu

DOI: 10.1111/j.1532-5415.2010.02806.x

JAGS 58:895–900, 2010
© 2010, Copyright the Authors
Journal compilation © 2010, The American Geriatrics Society
0002-8614/10/$15.00
scores on a digit–symbol test of complex attention and cognitive speed in caregivers of spouses with dementia (than for non-caregiving controls) were no longer significant after controlling for subjective stress.11 This suggests that distress explains the link between exposure and adverse cognitive outcomes in spouses of persons with dementia. The Nurses Health Study showed that women caring for an ill or disabled spouse performed worse than women who were not providing care on a general cognitive screening test.12 One longitudinal study found that decline in vocabulary over a 2-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. One study found that caregivers of spouses with dementia had significantly worse general cognitive functioning than controls.14 Another demonstrated that caregivers of relatives in palliative care exhibited significantly greater cognitive impairment than a control sample.15 After the death of a 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.” Another study recently showed that caregivers of spouses with dementia scored lower on a digit symbol test than non-caregiving controls at baseline, and declined 4.5 times as fast as non-caregivers over 2 years.16 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.

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 are reported here. A careful dementia ascertainment protocol was used 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. It was hypothesized that older married adults would be at greater risk for incident dementia after onset of dementia in their spouse. Given that female caregivers are significantly more likely to report poor well-being,17 depression, and anxiety18 than male caregivers, whether the effect of having a spouse with dementia would be greater for women than men was explored.

METHODS
The current report uses extant data from the Cache County (Utah) Study (CCS) on Memory Health and Aging. The institutional review boards of Utah State University, Duke University, and The Johns Hopkins University approved study procedures. 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, all 5,756 permanent residents of the county aged 65 and older were invited to join the study; 5,092 (90%) agreed to a baseline interview. Three thousand two hundred ninety-nine (3,299) were married, 1,534 widowed, 167 divorced or separated, and 82 never married; 10 had unknown marital status. Of married respondents, 2,738 (83%) had a spouse who was also a CCS participant. The present work focuses on married couples in which 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 10 couples (0.4%), one spouse resided in a nursing home at baseline. 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 ± 3.1 years—5.1 ± 3.2 years before and 4.1 ± 3.2 years after their spouse’s dementia onset. Unexposed participants were followed slightly longer (mean 4.5 ± 4.2 years).

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

Clinical Evaluation of Dementia
The CCS used a multistage dementia ascertainment protocol repeated in four waves (1995/97, 1998/2000, 2002/04, and 2005/07). Briefly, screening began with an in-person interview including the modified Mini-Mental State Examination (3MS) or, for those unable to participate, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Participants whose screening scores suggested possible dementia then completed an in-depth clinical assessment (CA), as did a 19% designated subsample. 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 1-hour battery of neuropsychological tests.

A geriatric psychiatrist and neuropsychologist, along with the assessment team, reviewed these data and assigned working Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, (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). This missing data problem was addressed by imputing dementia status, based on 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) before being assigned to undergo a CA. DQ interviews were rated as 1 = cognitively normal, 2 = mild, 3 = moderate, 4 = severe cognitive impairment, or 5 = dementia.

When DQ results were available, these scores were relied on 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 absent in others. When no DQ was available, screening data were used; if the IQCODE score was 3.6 or higher (sensitivity was present in subjects with a DQ rating of 5 and absent in others). With imputed dementia were assumed to have experienced dementia onset midway between the point at which DQ or screening data were used for imputation and the prior wave of normal cognitive status. In combination, these strategies enabled 1,092 person-years of observation to be considered that would otherwise have been ignored. Of the 253 subjects with incident dementia, 203 (80%) were diagnosed clinically and the rest by imputation.

Covariates

Analyses considered participants’ sex and age at baseline. Additionally, the models adjusted for apolipoprotein E (APOE) genotypes obtained at baseline. To at least partially control for shared environmental exposures that might influence risk for dementia in both spouses, socioeconomic status (SES), a significant predictor of many health-related outcomes including dementia, was adjusted for. Couple-level SES was measured using the husband’s education and occupation. Occupation of longest duration was coded into nominal categories of professional, technical, managerial; clerical and sales; service; agricultural; and machine or miscellaneous. The statistical dependence between spouses within a couple was also addressed using random effects modeling, as described below.

Data Analysis

A series of Cox proportional hazards regression models was estimated to examine the association between having a spouse with dementia, a time-varying covariate, and subsequent risk for incident dementia. 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 according to baseline age group (<75, 75–85, 85+); thus, the parameter estimate for “age” in the models reflects the general effect of each additional year of age within each age stratum.

Observation Time

To model time to incident dementia, each participant’s observation time started at baseline screening and ended at year of dementia onset, right-censoring, or the spouse’s right-censoring (death or loss to follow-up), whichever happened first. When the spouse’s right-censoring event occurred first, it was decided to end the index subject’s observation, which was a conservative approach to address the unknown exposure thenceforward.

Exposure Time

Onset of exposure to having a spouse with dementia was dated 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 care recipient with dementia, an approach of “once exposed, always exposed,” (the exposure variable was not “reset” to “no exposure” after death of the the care recipient) was used.

Adjustments for Widowhood and Dependent Observations within Dyads

Because few unexposed subjects (0 men, 4 women) were widowed over the entire period of observations, potential confounding effects of widowhood could not be adjusted for, although there was concern 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, Cox proportional hazard models were fit that allowed for random effects. In this application, random effects represent the influence of shared unmeasured (but present nonetheless) factors that affect the hazard rate for dementia for both spouses in a couple. Models that include random effects directly address the problem of statistical dependence between 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 with those reported here. Additionally, separate models were fit according to sex to allow individual examination of the effects of having a husband with dementia versus a wife.

RESULTS

The mean age of husbands was 75.7 ± 5.9, and that of wives was 73.1 ± 5.3. Prior duration of marriage at baseline averaged 48.9 ± 11.5 years, with only 40 (3.8%) 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. Tables 1 and 2 provide sample characteristics along with results of tests of bivariate relationships. As expected, incident dementia was significantly associated with each of the following: older age, presence of one or more APOE ε4 alleles, and having a spouse with dementia.
mentia in one's spouse (HRR = 11.9, 95% CI = 1.7–85.5) than women (HRR = 3.7, 95% CI = 1.2–11.6) (Table 3). Additional models (not shown) adjusted for length of marriage at baseline and its interaction with exposure to having a spouse with dementia (interaction was nonsignificant), with negligible influence on effect of this exposure, for husbands and wives.

DISCUSSION

To the authors’ knowledge, this is the first population-based sample used to study risk for incident dementia in married older adults as a function of whether the spouse develops incident dementia. The finding of a six times greater risk of dementia in persons so exposed than in married men and women whose spouse had not developed dementia remained after adjustment for age, sex, education, SES, and APOE genotype, all of which were (as expected) associated with dementia risk. Length of marriage did not modify this association. The 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 risk for depression and mortality. Having a loved one with dementia is stressful regardless of age, but the burden for spouses may be even greater because of close emotional ties to their partner, their own medical comorbidity, greater risk for functional limitations, and greater likelihood of fatigue with physical exertion. Neuropsychiatric disturbances that are common over the course of dementia are particularly stressful and are the most common reason for institutionalization. Anticipatory grief (related to loss of predementia relationship as dementia progresses with spouse’s impending death) has been independently associated with caregiver burden in dementia caregivers beyond effects of caregiver characteristics and behavior problems in the care recipients.

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. The models adjusted for SES, 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, although the 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 similarity in proneness to distress or mental illness may influence shared risk for dementia in couples. Thus, although the overall risk for dementia in 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

### Table 1. Bivariate Relationships Between Categorical Independent Variables and Incident Dementia

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Developed Incident Dementia, n (%)</th>
<th>Chi-Square P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having a spouse with dementia</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Exposed (n = 229)</td>
<td>34 (14.8)</td>
<td></td>
</tr>
<tr>
<td>Nonexposed (n = 2,213)</td>
<td>221 (10.0)</td>
<td></td>
</tr>
<tr>
<td>Number of subject apolipoprotein E e4 alleles</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>0 (n = 1,629)</td>
<td>147 (9.0)</td>
<td></td>
</tr>
<tr>
<td>1 (n = 710)</td>
<td>85 (12.0)</td>
<td></td>
</tr>
<tr>
<td>2 (n = 65)</td>
<td>22 (33.8)</td>
<td></td>
</tr>
<tr>
<td>Husband’s occupation*</td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>Professional, tech., mgt (n = 1,038)</td>
<td>100 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Clerical, sales (n = 198)</td>
<td>20 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Service (n = 70)</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>Agriculture (n = 518)</td>
<td>61 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Machine or miscellaneous (n = 618)</td>
<td>65 (10.5)</td>
<td></td>
</tr>
</tbody>
</table>

* Subject’s own if male and spouse’s if female.
† Number and frequency suppressed to comply with privacy policy of Centers for Medicare and Medicaid Services.

An unadjusted proportional hazards regression model of survival time to incident dementia revealed a substantially greater hazard for dementia after spouse’s dementia onset, with a hazard rate ratio (HRR) of 6.4 (95% confidence interval (CI) = 2.4–17.2, P < .001). In the fully adjusted model (Table 3), older age and presence of at least one APOE e4 allele (in relation to no e4 allele) were associated with higher risk of incident dementia, whereas higher SES (husband with professional, technical, or managerial occupation) was associated with less 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, 95% CI = 2.2–16.2, P < .001). (When models were repeated without imputation for dementia in participants with incomplete ascertainment, the effect of having a spouse with dementia was comparable: HRR = 7.7, 95% CI = 1.9–31.3, P = .004.)

In analyses stratified according to sex, the effect of exposure to dementia in one’s spouse was higher for men

### Table 2. Bivariate Relationships Between Continuous Independent Variables and Incident Dementia

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Incident Dementia (n = 255)</th>
<th>No Dementia (n = 2,187)</th>
<th>T-Test P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject age at baseline</td>
<td>75.9 ± 5.8</td>
<td>74.2 ± 5.8</td>
<td>.001</td>
</tr>
<tr>
<td>Spouse age at baseline</td>
<td>74.7 ± 6.2</td>
<td>74.4 ± 5.7</td>
<td>.40</td>
</tr>
<tr>
<td>Husband’s education, years*</td>
<td>13.8 ± 3.3</td>
<td>14.0 ± 3.4</td>
<td>.51</td>
</tr>
</tbody>
</table>

* Subject’s own if male and spouse’s if female.
Table 3. Risk of Incident Dementia in 2,442 Married Older Adults as a Function of Whether Spouse Had Dementia, Adjusted for Covariates: Total Sample and Stratified According to Spouse’s Sex

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Total Sample</th>
<th>Husband as Index Subject</th>
<th>Wife as Index Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having spouse with dementia</td>
<td>6.01 (2.23–16.17)</td>
<td>11.93 (1.67–85.52)</td>
<td>3.66 (1.15–11.61)</td>
</tr>
<tr>
<td>Female</td>
<td>0.80 (0.61–1.03)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Age at baseline interview</td>
<td>1.06 (1.01–1.12)</td>
<td>1.02 (0.98–1.07)</td>
<td>1.15 (1.06–1.24)</td>
</tr>
<tr>
<td>Number of apolipoprotein E ε4 alleles (reference: 0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.45 (1.11–1.90)</td>
<td>1.42 (1.00–2.02)</td>
<td>1.55 (1.01–2.38)</td>
</tr>
<tr>
<td>2</td>
<td>4.54 (2.86–7.23)</td>
<td>4.91 (2.74–8.79)</td>
<td>3.83 (1.68–8.72)</td>
</tr>
<tr>
<td>Husband’s occupation (reference: machine, miscellaneous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional, technical, management</td>
<td>0.64 (0.44–0.93)</td>
<td>0.67 (0.41–1.09)</td>
<td>0.56 (0.30–1.04)</td>
</tr>
<tr>
<td>Clerical, sales</td>
<td>0.66 (0.40–1.10)</td>
<td>0.57 (0.28–1.15)</td>
<td>0.79 (0.38–1.66)</td>
</tr>
<tr>
<td>Service</td>
<td>0.98 (0.48–2.01)</td>
<td>1.01 (0.41–2.50)</td>
<td>0.67 (0.19–2.31)</td>
</tr>
<tr>
<td>Agriculture</td>
<td>0.81 (0.57–1.15)</td>
<td>0.93 (0.60–1.46)</td>
<td>0.59 (0.33–1.06)</td>
</tr>
<tr>
<td>Husband’s education, years</td>
<td>1.00 (0.95–1.05)</td>
<td>1.00 (0.94–1.06)</td>
<td>1.00 (0.93–1.08)</td>
</tr>
</tbody>
</table>

adverse effects of the exposure. Results of such analyses would then guide possible interventions.

Study strengths include a large community-based sample that avoided the selection bias of clinical samples and availability of APOE genotypes. Its high baseline participation rate (90%) reduced concerns about nonresponder bias. 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
These results are consistent with other studies demonstrating cognitive deficits in spouses of persons with dementia and extend the findings to include incident dementia risk. A clear greater risk of incident dementia in older adults whose spouses have dementia was found, but further study is needed to isolate specific mechanisms, identifying particular vulnerabilities in 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 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.

ACKNOWLEDGMENTS
Dr. Welsh-Bohmer and Dr. Breitner developed the neuropsychological testing and clinical assessment procedures. Dr. Tschanz provided training and oversight of all field staff and reviewed all individual neuropsychological test results to render professional diagnoses. The board-certified or board-eligible geriatric psychiatrists or neurologists who examined the study members included Drs. Steinberg, Breitner, Lyketsos, Gagliardi, Raj, Christopher, and Green. Dr. Williams also examined several subjects and provided expert neurologic consultation. Dr. Townsend conducted autopsy examinations. Ms. Leslie coordinated the autopsy enrollment program. Diagnosticians at the expert consensus conferences included Drs. Breitner, Burke, Lyketsos, Plassman, Steffens, Steinberg, Toohill, Tschanz, and Welsh-Bohmer. We acknowledge the additional contributions of the following individuals whose activities have helped to ensure the success of the project: Cara Brewer, BA, Tony Calvert, BSC, Carol Leslie, MS, Georgiann Sanborn, MS, Michelle McCart, Heidi Wengreen, PhD, RD, James Wyatt, and Peter P. Zandi, PhD, MPH, Roxane Pfister, MS, Nancy Sassano, PhD.

Conflict of Interest: None of the authors has any financial or personal conflicts of interest, or relationships and affiliations relevant to the subject of this manuscript.

This work was supported by National Institutes of Health Grants AG-031272, AG-011380, and AG-021136.

Author Contributions: Dr. Norton had full access to all the data and takes responsibility for data integrity and accuracy of the data analysis. Dr. Norton and Dr. Tschanz: obtaining funding; conception and design; acquisition, analysis, and interpretation of data; preparation of manuscript. Dr. Smith, Dr. Østbye, and Dr. Corcoran: conception and design, analysis and interpretation of data, preparation of manuscript. Ms. Schwartz: data file creation and statistical analysis, preparation of manuscript. Dr. Percy, Dr. Rabins, Dr. Skoog: conception and design, preparation of manuscript. Dr. Steffens: conception and design, acquisition of data, preparation of manuscript. Dr. Breitner and Dr. Welsh-Bohmer: obtaining funding, acquisition of the data, preparation of manuscript.

Sponsor’s Role: Provision of funding to support data collection, analysis, interpretation, and manuscript preparation.
REFERENCES


