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An Ironic Tragedy: Are Spouses of Persons with Dementia at Higher Risk for Dementia than Spouses of Persons without Dementia?

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This issue of JAGs includes a paper by Norton et al. (2010)[1] that reports a 600% greater risk of dementia in spouses of persons with dementia relative to spouses of persons without dementia even after controlling for important risk factors for dementia. The authors explain their provocative finding using three arguments previously employed to understand the higher risks of health problems seen in spouses of persons with dementia relative to spouses of persons without dementia. These include assortative mating, a shared life-style, and caregiving.[2] However, no caregiver data are presented to support their argument (e.g., hours of care, length of care, caregiver distress, health habits and health problems); and this study was not designed to test the hypothesis that caregiving is a risk factor for dementia. Despite these limitations, many of the spouses of persons with dementia were probably caregivers; and, although it is not possible to conduct mediation analyses to interpret this study's result, the literature includes several caregiver outcomes that may be postulated as reasons for the observed higher dementia risk in spouses of persons with dementia.

Thousands of articles have reported greater psychological and/or physical health problems in caregivers relative to non-caregivers[2, 3]; however, it was not until 2003 that cognition was compared in caregivers versus non-caregivers. Norton et al.[1] present much of this research to support their finding. Importantly, two of these articles observed greater cognitive decline in caregivers relative to demographically-similar non-caregivers and these differences were mediated by variables salient to dementia. Greater two year decline in vocabulary in caregivers versus non-caregivers was mediated by caregivers having greater composite scores for obesity, fasting insulin, and fasting glucose than non-caregivers; and, a 4.5 faster two-year decline in processing speed in caregivers versus non-caregivers was mediated by higher depressed mood in caregivers than non-caregivers. Caregivers in these samples also declined 85% faster on self-rated physical functioning than did non-caregivers after controlling for functioning at study entry and important covariates. This was mediated by processing speed at study entry, processing speed decline from study entry to one year later, psychological distress at study entry, C-Reactive Protein (CRP) and increases in CRP from study entry to two years later.[4]

There are several other putative intervening variables between caregiving and incident dementia that should be considered. The first domain includes *Psychosocial and Behavioral*

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Risk Factors. Spouse caregivers of persons with dementia are more likely to have greater depressed mood than demographically-similar spouse non-caregivers [3] and they report poorer sleep quality than do non-caregivers.[5] Depressed mood is a potential risk factor for dementia [6], as are sleep problems [7]. Caregivers may also be more socially isolated and lonelier than non-caregivers [8] and these experiences are associated with less social engagement and less stimulating cognitive activities which may increase the risk for dementia.[9] Caregivers also report greater daily calorie and fat intake[2], less physical inactivity[10] and less time to exercise[11] than do non-caregivers. Poor diet and less physical activity may increase the risk for dementia [12, 13].

The second domain of putative mediators includes interrelated *Physiological Risk factors*. In a meta-analysis of family caregivers of persons with dementia versus non-caregivers who were similar in age, gender, and type of relationship, stress hormones had the largest mean effect size (r = .23) of 11 health categories[2]. This is important because elevated levels of cortisol are associated with less hippocampus volume and brain glucose metabolism[14]. Insulin is critical to brain regions involved in learning/memory[15, 16] and hyperinsulinemia is associated with greater dementia risk[17–19]. Similarly, caregivers have greater weight gain, waist size, and/or obesity than non-caregivers[20–22]. Importantly, 73 caregivers of persons with AD had higher fasting insulin levels at study entry and 15–18 months later than did 69 demographically-similar non-caregivers even after obesity, exercise, gender, age, alcoholic drinks, hormone replacement therapy, lipids, and hypertension were controlled in the analyses[23]. Higher fasting insulin levels were also observed in another study of 123 spouse caregivers of persons with AD than 117 spouse non-caregivers at study entry, one year, and two years later, after adjusting for covariates [21].

These results may be noteworthy because insulin resistance is associated with greater cerebral inflammation and amyloid-beta protein levels which form the “plaques” seen in AD[24]. Alternatively, reductions in stressors may decrease pro-inflammatory cytokine levels (interleukin-6; IL-6) [25] and depression and stressful experiences may increase pro-inflammatory cytokines[26]. In response to circulating proinflammatory cytokines the liver releases CRP which harms artery linings. Elevated CRP levels may also increase the risk for dementias[25]. Insulin resistance can damage blood vessels, diminish cerebral blood flow and promote inflammation[27]. The results of these studies are important for dementia risk in caregivers because IL-6 serum levels increase over six-years in caregivers at a rate that is 400 percent higher than in age-matched non-caregivers. [28] Also, caregivers increase in CRP over two years significantly more than do non-caregivers despite having similar levels at study entry[4]. Caregivers of persons with AD also have significantly higher plasma D-dimer levels (i.e., intravascular thrombosis) than non-caregivers[29]. Finally, over six years of follow-up, caregivers who provide the most assistance to their spouses with AD, have the greatest hazard of reaching at least one frank cardiovascular event relative to other caregivers and non-caregivers[30].

Another major finding of the current paper is that “the association of spousal dementia with subsequent dementia in the caregiver was stronger for husbands ‘caring for’ wives with dementia than for wives ‘caring for’ husbands with dementia”. Although this was contrary to what Norton et al.[1] predicted, it is what one would have predicted given the literature. Men have higher rates of chronic illnesses and less longevity than women; and widowers have more illnesses, and higher rates of mortality than widows. Men also have greater physiological reactivity to laboratory stressors than do women which may be exacerbated when faced with caregiving [2]. Indeed, men caregivers are more physiological reactive to laboratory stressors than women caregivers or men non-caregivers [2]. Men caregivers also have lower high density lipoproteins than men non-caregivers, but this is not true for women caregivers versus women non-caregivers[2]. This may be important because elevated

cholesterol is a risk factor for dementia. Given this literature, one would have expected the difference in Hazard Rate Ratios (HRRs) for caregivers versus non-caregivers to be significantly different for men and women. However, Norton et al.[1] reported them as not significantly different using the method of overlapping confidence intervals. Unfortunately, when the null hypothesis is false this method mistakenly fails to reject it (e.g., no gender differences in HHRs) more frequently than a formal test. As the authors note, replications with larger samples of men are in order.

In conclusion, to interpret and extend the current results, future work should address several issues. First, during this study's follow-up, incident dementia was 14.8% for spouses of persons with dementia and 10.0% for spouses of persons without dementia. However, when the authors incorporated into their analysis the amount of time that a spouse was exposed to her/his spouse's dementia, the added risk increased from 48% to 600%. This occurred even after adjusting for age, gender, education, socio-economic status and the presence of at least one Apolipoprotein E ε4 allele (versus no ε4 allele).

We need to understand how length of exposure and its interactions with demographic, psychosocial, behavioral and physiological variables serve to increase the dementia risk so dramatically. For example, age may exacerbate dementia risk in caregivers because it is associated with increases in cortisol levels, chronic inflammation and dementia incidence. Caregivers who are older prior to exposure may be at greater risk for chronic diseases, neurological problems and acute events (e.g., strokes) than older non-caregivers, but such differences may not be as great for younger caregivers and non-caregivers. Hence, length of exposure may be more serious for older than younger spouse caregivers. Such differences could have major implications for preventing dementia in younger caregivers. Ethnicity is also relevant to caregiver dementia risk because it is related to health disparities and caregiver distress.[2] In the current paper the ethnic composition of the Cache County sample is not provided, but the county is reported to be 92% white, with very small percentages of Asian-, Native-, and African-Americans. As such, it is unclear to what degree the added dementia risk for spouses of persons with dementia versus spouses of persons without dementia exists for other Americans.

Finally, several factors may confer a higher dementia risk in spouse caregivers than spouse non-caregivers, but many of them probably share similar pathological processes and are predictive of similar illnesses. Hence, repeated associations of putative risk factors with incident dementia are only necessary and not sufficient conditions for causality. It may be difficult to distinguish prognostic factors, causal intervening variables, and symptoms of pre-clinical dementia, e.g., inflammation is associated with dementias, depression, diabetes, coronary disease, obesity and AD.[31] Research must determine whether inflammation prior to dementia is an early independent predictor, contributing factor or simply a preclinical effect of slowly evolving dementias. [32] To better understand such relationships it may be necessary to perform doubly-prospective studies. These could examine several potential intervening variables simultaneously before and after the incidence of caregiving and the incidence of dementia, and test for mediation by examining changes in putative intervening variables relative to incident caregiving and incident dementia. Despite potential confounding of risk factors with actual causes of dementia, we present these factors here because data suggest they are more likely to occur in spouse caregivers than spouse non-caregivers and they may be predictive of dementia. In sum, rather than being alarmed by the results reported here [1], stake holders, policy makers, clinicians, and researchers should be motivated to support and design appropriate studies which if proved positive, can be used to plan interventions and preventions to prepare for the projected increases in dementia expected in the decades ahead.

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