ARIC Manuscript Proposal #3824

PC Reviewed: 4/13/21   **Status:** _____   **Priority:** 2
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: Cognitive Decline and Dementia Risk among Spouses of People with Dementia: Shared Environment or Caregiver Stress?

b. Abbreviated Title (Length 26 characters): **Spouses & Dementia Risk**

2. Writing Group:
Writing group members: Mark Lee, Ryan Demmer, Anna Kucharska-Newton, B. Gwen Windham, Priya Palta, Tetyana Shippee, Pamela L. Lutsey

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ML___ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Data analysis will begin after approval.

4. Rationale:

An estimated 16 million Americans provide unpaid care for people living with Alzheimer's Disease and AD-related dementia in the United States.[1] Caregiving responsibilities frequently

fall to the spouse of a person with dementia. Although there are some perceived benefits to caregiving,[2] much research documents the social, emotional, financial, and physical burdens that caregivers of people with dementia face.[3–6] Notably, several studies have shown that spouse caregivers of people with dementia have lower cognitive functioning and higher risk of dementia than non-caregiving spouses.[7,8] The experience of these caregivers is unique: one study reported that spouse caregivers of people living dementia compared to spouse caregivers of people without dementia experienced steeper cognitive decline during the years leading up to and following the death of their spouse.[9] However, the reasons for this association are not clear.

One possible explanation for why having a spouse with dementia is associated with increased dementia risk is shared environment. Mid-life social and behavioral factors including low education, hypertension, smoking, diabetes, physical inactivity, and obesity are strongly related to late-life dementia risk.[10] Because of assortative mating and partner influence, spouses tend to be concordant on these risk factors.[11–16] Therefore, the spouse of a person with dementia may have increased dementia risk because both individuals share a common elevated risk profile.

An alternative explanation for the association of dementia risk between spouses is caregiver stress.[17] Among caregivers of people with dementia, 59% reported high emotional stress and 38% reported high physical stress.[1] This stress is chronic, with people frequently living 4-8 years following a dementia diagnosis, and some live for much longer.[18] Chronic caregiver stress has well-known physiological and behavioral consequences, including isolation, depression, sleeping problems, hypertension, weight change, smoking, and alcohol consumption.[17,19–24] These sequelae of caregiving stress could increase dementia risk among spouses of people with dementia.

To date, there has been no published research adjudicating shared environment and caregiver stress as drivers of the relationship between spouse and spouse caregiver's dementia risk. From a public health and clinical perspective, it is important to distinguish between these pathways. If shared environment is confounding the relationship, that would suggest that behavioral and lifestyle interventions in mid-life aimed at reducing dementia risk should target both individuals and their spouses to have maximal impact. On the other hand, if caregiver stress and subsequent physiological and behavioral changes mediate the relationship, interventions should be developed to mitigate these negative impacts among caregivers.

Gender may moderate the additional dementia risk posed by caring for a spouse with dementia. A recent systematic review reported that female caregivers report greater burden and higher levels of depression than male caregivers.[25] Qualitative evidence suggests that this is related to gendered role expectations in spousal caregiving: wives are more likely to bear the burden of care themselves while husbands act as care managers and are more likely to seek help.[26] To the extent that these gendered approaches to caregiving produce different stress responses, wives may be more affected by their husbands' cognitive status than vice versa. Empirically examining gender modification in this relationship is important for identifying populations at elevated risk and developing targeted interventions. However, there is limited research to date on this topic.

To answer these important questions, we will rely on prospective data from spouse pairs in ARIC. The ARIC cohort, at baseline, included 4,507 heterosexual spouse pairs. Of these 1,406

pairs (2,812 individuals) participated in ARIC visit 5. This unique feature of the cohort allows us to estimate dementia risk posed by having a spouse with dementia. Rich mid-life measures (including education, smoking, obesity, diabetes, hypertension, and physical activity) and late-life measures (including smoking, alcohol consumption, physical activity, hypertension, and depression) make it possible to test shared environment and caregiver stress as potential drivers of this relationship. Because the spouse pair sample includes an equal number of men and women at baseline, it is also possible to test for gender modification.

Figure 1 depicts the hypothesized relationships in the model and when they will be measured in ARIC. We predict that there will be a significant association between spouse's cognitive status (i.e. having dementia, assessed at Visit 5) and incident dementia for the index participant (measured between Visits 5 and 7). The shared environment model hypothesizes that this association is explained by *pre-existing* social and behavioral risk factors that are correlated within spouse pairs (measured at Visit 1, before either spouse had dementia). On the other hand, the caregiver stress model hypothesizes that having a spouse with cognitive impairment induces a stress response in the index participant, evidenced by contemporaneously measured behavioral and psychological factors. These late-life factors mediate the relationship between spouse's cognitive status and the index participant's dementia risk.

Figure 1. *Model diagram depicting how shared environment and caregiver stress could explain the relationship between spouse's cognitive status and index participant's dementia risk.*
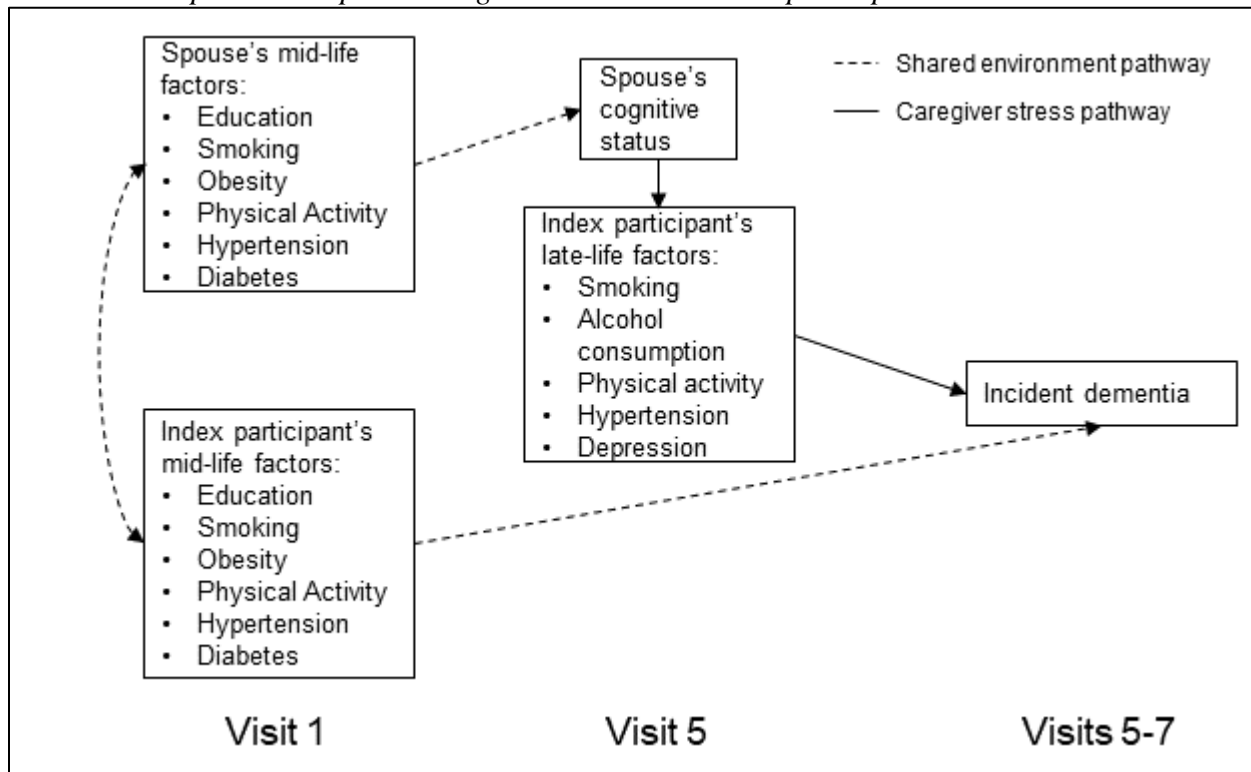
5.   Main Hypothesis/Study Questions:

Study questions:

1. Is having a spouse with dementia/mild cognitive impairment associated with elevated dementia risk?
2. To what extent do shared environment and caregiver stress explain the concordance between spouses' dementia risk?
3. Does gender moderate the dementia risk associated with having a spouse with dementia/mild cognitive impairment?

Hypotheses:
1. Having a spouse with dementia/mild cognitive impairment is associated with elevated dementia risk.
2. Adjusting for mid-life risk factors (i.e., education, smoking, obesity, physical activity, hypertension, diabetes) partially explains the elevated dementia risk associated with spousal dementia/mild cognitive impairment.
3. Adjusting for late-life risk factors (i.e., smoking, alcohol consumption, physical activity, hypertension, depression) partially explains the elevated dementia risk associated with spousal dementia/mild cognitive impairment.
4. The elevated dementia risk associated with spousal dementia/mild cognitive impairment is greater for wives than husbands.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: This study will use prospective cohort data from ARIC Visit 5 (2011-2013) through Visit 7 (2018-2019) or latest follow-up available.

Inclusion/Exclusion: We will include all spouse pairs who participated in Visit 5. We will exclude participants who did not identify as Black or White, those who are missing data for key covariates, and those who have prevalent MCI or dementia at Visit 5.

Outcome: Incident dementia ("level 3") from Visit 5 through Visit 7 as determined according to current ARIC-NCS analysis recommendations.

Exposure variable:
Spouse dementia/MCI: Information on spousal dementia/MCI will be according to ARIC-NCS dementia classification. The primary analysis will use spousal cognitive status (dementia/MCI/normal) at the time of ARIC visit 5. Of the 2,020 individuals who are cognitively normal at Visit 5, 426 are married to person with MCI and 94 are married to a person with dementia. In secondary analyses, we will model spousal dementia status as a time-varying exposure.

Covariates: All covariate information will come from the index spouse, in whom we are trying to predict dementia risk.

All models will adjust for demographic covariates including race, gender, field site, and age at visit 5.

Covariates related to the <u>shared environment</u> between spouses (measured at Visit 1) include: education (<high school, high school, college), smoking (never, former, current), obesity (BMI <30 kg/m^2 vs. BMI ≥30 kg/m^2), physical activity (≥150 min/week of moderate OR ≥75 min/week of vigorous exercise vs. less than this amount), diabetes (determined by fasting blood glucose, self-reported diagnosis, and/or current use of antidiabetic medication), and hypertension (SBP ≥140 mm Hg OR DBP ≥90 mm Hg vs. lower).

Covariates related to <u>caregiver stress</u> (measured at Visit 5) include: smoking (yes or no), alcohol consumption (0-14 drinks/week vs. >14 drinks/week), physical activity ((≥150 min/week of moderate OR ≥75 min/week of vigorous exercise vs. less than this amount), hypertension (SBP ≥140 mm Hg OR DBP ≥90 mm Hg vs. lower), and depression (determined by CES-D score).

Effect Modifier: To answer our 3rd study question, models will be stratified by sex.

Statistical Analysis: This study will use Cox proportional hazard models to estimate the effect of spousal dementia/MCI on dementia risk. The primary analysis will use spousal cognitive status (dementia/MCI/normal) at the time of ARIC visit 5. As noted above, <u>all</u> covariate information will come from the index spouse, in whom we are trying to predict dementia risk. In secondary analyses, we will model spousal dementia status as a time-varying exposure to account for the fact that some spouses had incident dementia between visits 5 and 7. To account for the correlation between spouse pairs, we will include random effects for each family, following Norton et al.[8] To test our first hypothesis, Model 1 will estimate the effect of spousal dementia/MCI on dementia risk after adjusting for demographic covariates (race, gender, field site, and age at Visit 5). To test our second hypothesis, Model 2 will add shared environment covariates (education, smoking, obesity, physical activity, diabetes, and hypertension at Visit 1) to Model 1. To test our third hypothesis, Model 3 will add covariates indicating caregiver stress (smoking, alcohol consumption, physical activity, hypertension, and depression at Visit 5) to Model 2. To test our fourth hypothesis, we will repeat this sequence of models in samples stratified by sex. We will follow VanderWeele and colleagues' methods for conducting mediation analysis to formally test our hypotheses.[27,28] The proportional hazards assumption will be tested by including cross-product terms in the models.

Limitations: Updated information on marital status is not available. Therefore, it is possible that some of the spousal pairs identified as such at baseline are now divorced, yet both partners still attended ARIC visit 5. However, although the divorce rate among middle-aged and older adults has grown in recent decades, it was relatively low in the 1980s when this cohort was recruited and continues to be less common than divorce among younger adults.[29] An additional limitation is that ARIC does not collect data about spouse caregiving responsibilities, so we assume that anyone married to a person with dementia does at least some caregiving. We will conduct robustness checks to see if our results hold after accounting for the fact that some spouses receive formal care in a nursing home. It is possible that the sample size, particularly for sex-stratified analyses, will be too small.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes   __X__ No

b. **If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No**
(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

___X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

There are currently no manuscript proposals using the spouse pair data in ARIC in relation to dementia.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal
_X__ **A. primarily the result of an ancillary study (list number* 2008.06)**
___ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)**

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in

http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms.
http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals
automatically upload articles to PubMed central.

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