

# Social Network, Cognitive Function, and Dementia Incidence Among Elderly Women

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Emerging evidence suggests that social support networks may have a positive influence on cognition and a protective association with the development of dementia among older adults. Although some studies found no association between social networks,<sup>1</sup> social engagement,<sup>2</sup> or marital status<sup>3,4</sup> with cognition, more-recent studies have suggested the protective effect of social engagement,<sup>5–7</sup> social support,<sup>8,9</sup> social contact,<sup>10</sup> social network,<sup>11</sup> and social activities<sup>12</sup> on cognitive function.

Dementia cannot be determined without assessing cognitive function and can be seen as the lowest end of the continuum of cognitive function. Some previous studies examined the association of social networks with cognitive function or with dementia. Bassuk et al.<sup>13</sup> found, after they controlled for a variety of risk factors, that those with no social ties had a more than 2-times increase in risk of being cognitively impaired compared with those who had 5 or 6 social ties. Fratiglioni et al. found that living alone and having no close personal ties nearly doubled the risk of developing dementia over 3 years.<sup>14</sup> Saczynski et al. found that decreased social engagement from midlife to late life was associated with dementia risk.<sup>15</sup> Seeman et al. determined that emotional support at entry into their study was an independent predictor of better maintenance of cognitive functioning at the 7.5-year follow-up.<sup>16</sup> Each of these studies used different cognitive tests and social network measures, making comparison of results difficult.

We expanded on these previous studies by recruiting a large elderly sample population and applying widely used and validated measures of social network and cognition. Our substudy of the Women's Memory Study gathered information annually from 2001 through 2005 to determine the relationship of social network to cognitive function and the development of dementia.

**Objectives.** We examined whether social networks had a protective association with incidence of dementia among elderly women.

**Methods.** We prospectively studied 2249 members of a health maintenance organization who were 78 years or older, were classified as free of dementia in 2001, and had completed at least 1 follow-up interview in 2002 through 2005. We used the Telephone Interview for Cognitive Status–modified, the Telephone Dementia Questionnaire, and medical record review to assess cognitive status. We used the Lubben Social Network Scale–6 to assess social network. We estimated hazard ratios for incident dementia with Cox proportional hazards models, adjusting for age at entry, education, hormone use, cognitive status scores, and health conditions.

**Results.** We identified 268 incident cases of dementia during follow-up. Compared with women with smaller social networks, the adjusted hazard ratio for incident dementia in women with larger social networks was 0.74 (95% confidence interval=0.57, 0.97).

**Conclusions.** Our findings suggest that larger social networks have a protective influence on cognitive function among elderly women. Future studies should explore which aspects of social networks are associated with dementia risk and maintenance of cognitive health. (*Am J Public Health.* 2008;98:1221–1227. doi:10.2105/AJPH.2007.115923)

## METHODS

### Participants

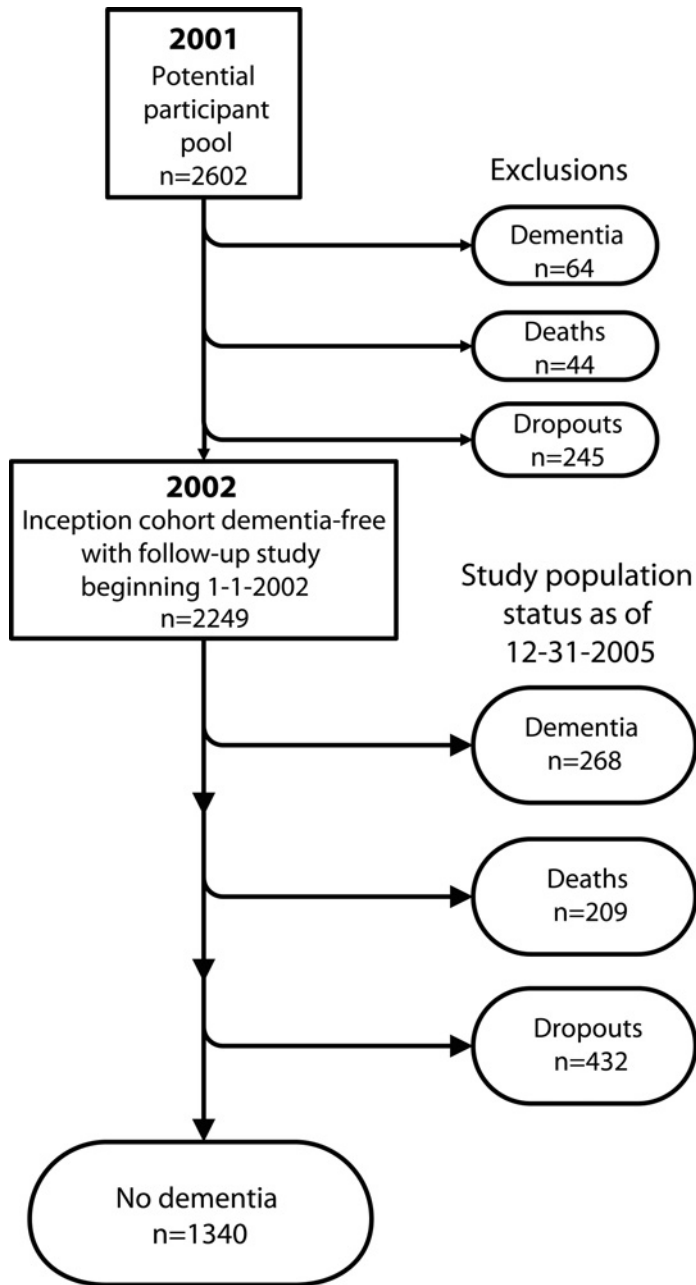
We recruited a cohort from a longitudinal study that examined the effect of hormone replacement therapy on the incidence of dementia among elderly women. Participants were part of a defined population of female members of Kaiser Permanente Southern California who were 75 years and older on July 1, 1998. We identified current hormone replacement therapy users (n=3058) and nonusers (n=3958), frequency matched by age and zip code, through computer-stored prescription data in the Kaiser Pharmacy Information Management System. Of these, 3924 women participated in telephone interviews to assess cognitive function in 1999. A detailed description of the original study population and procedures is available elsewhere.<sup>17</sup>

In 2001, the baseline year for our substudy, social network questions were added to the telephone interview, and 2602 women were interviewed. At that time, all participants were 78 years or older. During the enrollment process for our study, potential participants were excluded because of dementia

(n=64), death (n=44), refusal to participate or inability to contact (n=228), and incomplete social network interviews (n=17). Thus, we excluded 353 women, leaving 2249 women available for follow-up from the beginning of our study on January 1, 2002. Figure 1 illustrates the potential sample pool in 2001 and the final status of our participants, starting on January 1, 2002, and ending on December 31, 2005.

### Multistage Cognitive Assessment for Dementia

Classification of cognitive status was conducted in 3 stages. The first stage involved administration of the previously validated<sup>18</sup> 23-question Telephone Interview for Cognitive Status–modified (TICS–m). The TICS–m is similar to and strongly correlated with the Mini-Mental Status Examination.<sup>19–22</sup> The 12 areas scored included name, date, age, phone number, ability to count backward from 20 to 1, immediate recall of 10 words, serial 7s (counting backward from 100 by 7), the naming of objects and concepts, repetition of phrases, the naming of president and vice president, tapping on phone mouthpiece 5



**FIGURE 1—Final dementia status of a cohort of women 78 years and older followed in 2001–2005.**

times, naming opposites of common words, and delayed recall of 10 words (maximum score = 50 points). The psychometric properties of the computerized TICS–m in this study were also evaluated<sup>23</sup> and validated against neuropsychological tests.<sup>24</sup> Previous studies demonstrated that the TICS–m has

high sensitivity in the detection of dementia<sup>25,26</sup> but a low positive predictive value.<sup>18</sup>

The TICS–m has a 28-point cutoff score, with 99% sensitivity and 86% specificity for a dementia diagnosis.<sup>25</sup> TICS–m cutoff scores classify individuals as having no or minimal cognitive impairment (TICS–m score > 27) or

possible cognitive impairment (TICS–m score ≤ 27). We classified women with a TICS–m score of more than 27 as having no or minimal cognitive impairment for that year. Women with a TICS–m score of 27 or less were selected for the second stage of assessment, in which the Telephone Dementia Questionnaire (TDQ) was administered to a proxy.

The TDQ, a previously validated instrument,<sup>27,28</sup> asks a proxy identified by the participant 48 or fewer questions about the participant's cognitive function in several domains (e.g., memory, fluency, comprehension, orientation). Gallo and Breitner found that when the TDQ was used with the TICS–m, its specificity was 0.99.<sup>25</sup> In our study, the TDQ was reviewed independently by 3 investigators. We used a predefined protocol to assign participants to 1 of 3 categories: (1) dementia, (2) no or minimal impairment, or (3) possible cognitive impairment, uncertain. A participant classified as having dementia had memory deficits, impairment in 2 or more other cognitive domains, and functional impairment. We reviewed the independent classifications in a consensus conference. A consensus classification of dementia or no or minimal impairment was final for that interview year. For women with a consensus classification of uncertain and those without a TDQ we proceeded to the third stage of assessment.

In the final stage of assessment we reviewed medical records. We gave a participant a final classification of dementia if a diagnosis of dementia was recorded in her medical record; we categorized a participant as having cognitive impairment but uncertain dementia if her medical record mentioned cognitive impairment but not dementia. If there was no mention of either condition in her medical record, we classified a participant with TDQ data as having cognitive impairment and a participant without TDQ results as having no or minimal impairment.

The 3-stage classification method we used has been validated independently of previous validations of the TICS–m and the TDQ. The multistage approach to classification of cognitive status was compared with a “gold standard” assessment of dementia conducted at the University of Southern California Alzheimer's Disease Research Center.<sup>29</sup> When

compared with that comprehensive in-person examination and neuropsychological testing, the sensitivity of the multistage approach for dementia versus no dementia was 0.83 and the specificity was 1.00.

We carried out annual telephone interviews with the study participants until they were classified with dementia or died. Deaths were ascertained through family and interviewer reports and medical discharge records through 2005 and the California Death Index through 2004. The telephone interviews also included a variety of questions regarding social and demographic characteristics, lifestyle variables, and health conditions reported at the time of recruitment or at any time during follow-up.

### Assessment of Social Network

Our primary social network measure was the abbreviated Lubben Social Network Scale (LSNS-6). This measure uses 6 questions: 3 key questions evaluate the size of 3 different aspects of social network that are attributable to family ties and a parallel set attributable to friendship ties. The LSNS-6 assesses the size of the respondent's active social network (i.e., relatives or friends seen or heard from  $\geq 1$  times/month), perceived support network (i.e., relatives or friends who could be called on for help), and perceived confidant network (i.e., relatives or friends to whom the respondent could talk about private matters).

Each LSNS-6 question is scored on a 0 to 5 scale. The total score is an equally weighted sum of these 6 questions, with scores ranging from 0 to 30. We also summed the subscale scores for family and friends, with results ranging from 0 to 15.<sup>30</sup> Higher scores indicate larger social networks. The validated LSNS-6 has been used widely and has established a cutpoint of 12 for best overall sensitivity.<sup>31,32</sup> A validation study, conducted in 3 European cities with a sample of 7432 elderly men and women, found an overall Cronbach  $\alpha$  of 0.83 that was consistent across all cities.<sup>33</sup>

Because our study population differed in important ways from the populations in which the scale had been validated (e.g., it was exclusively female and older), we analyzed the psychometric properties of the LSNS-6 with data from our participants who provided information on social network in 2001. Factor analysis

showed factor structures that were very similar to those reported by Lubben et al. and yielded factors from the 2 subscales that also mirrored those reported in that study.<sup>33</sup> The Cronbach  $\alpha$  values from our study were 0.84 for the LSNS-6, 0.86 for the family subscale, and 0.82 for the friend subscale and were consistent with previous studies.<sup>31</sup>

The assessment also included a specific measure of frequency of social contact with family and friends. Participants were asked to report how often they had visits, phone calls, or mail from family and friends: less than weekly, weekly, 3 to 6 times a week, or daily. They were also asked to report (yes or no) whether they were satisfied with the amount of contact they had with family and friends.

### Analyses

Descriptive statistics were generated for demographic variables including age, education, marital status, ethnicity, hormone use, and a select list of health conditions. Follow-up years were calculated from the baseline year (2001) until the date of the interview that resulted in a classification of dementia, the date of last contact if the participant dropped out, or December 31, 2005, if the participant was alive, not classified as having dementia, and still participating when the study ended.

We used the Cox proportional hazards model to estimate crude hazard ratios (HRs) and 2 adjusted HRs for dementia. The first adjusted model controlled for selected demographic and health conditions that have been found to be risk factors for dementia (i.e., age, education, depression, stroke, myocardial infarction, diabetes, hypertension, and Parkinson's disease).<sup>34–41</sup> The second adjusted model further adjusted for a dichotomous TICS–m score (which reflected our cognitive classification process) and hormone use at baseline. We also estimated adjusted HRs for dementia for women who scored high on the LSNS-6 total scale (0–11 as the referent) and those scoring higher on the LSNS-6 family and friends subscales (0–5 as the referent) and for frequency of and satisfaction with contact. Exact 95% confidence intervals (CIs) were calculated for HR estimates. We performed the *t* test for social network score differences between hormone users and nonusers. Because marital status has often

been used as a proxy for social ties, we also analyzed a possible interaction of marital status with the LSNS-6 and dementia.

We performed the  $\chi^2$  test for statistical significance for women who stayed in the study versus those who did not (i.e., those who were not dead or classified as having dementia over the follow-up period) along key variables: TICS–m scores, LSNS-6 scores, demographic characteristics, and health conditions. In all analyses, we considered *P* at less than .05 to be statistically significant.

## RESULTS

We identified 268 newly occurring (incident) cases of dementia (12%) in the 2249 women who had social support information in 2001 and had 1 or more follow-up assessment. From 2002 to 2005, there were 209 deaths (9%), and 432 women dropped out of the study (19%; Figure 1).

We compared demographic characteristics and health conditions for women with and without dementia and estimated HRs for dementia. In 2001, the mean age of all women in the analysis was 80.6 years (SD=3.1). The mean age of women with dementia was 81.4 years (SD=3.6), and of women without dementia, 80.5 years (SD=3.0). Table 1 shows the number and percentage of dementia cases along with key variables. Crude HRs indicated that being older or less educated or having a stroke, diabetes, depression, or a lower score on the TICS–m increased the risk of dementia in this population.

Social network scores and daily frequency of contact were associated with dementia risk. The mean total social network score, the LSNS-6, was 16.2 (SD=5.3); the mean score for the family subscale was 8.4 (SD=3.2) and for the friends subscale, 7.7 (SD=3.5). The mean LSNS-6 score for the group without dementia was 16.4 (SD=5.3) and 14.4 (SD=5.6) for the group with dementia. Table 2 shows the crude and adjusted HRs for dementia according to measures of social network and social support. With the lower LSNS-6 cutoff score (0–11) as the referent, the partially adjusted HR for dementia on the LSNS-6 total was 0.63 (95% CI=0.48, 0.83). With the lower subscale cutoff score (0–5) as the referent, the partially adjusted HRs for dementia

**TABLE 1—Baseline Demographic Characteristics and Health Conditions of Elderly Women in 2001, and Incidence of Dementia and Crude Hazard Ratios for Dementia Through Follow-Up (2002–2005): Southern California**

	Study Population, No.	Participants Who Developed Dementia, No. (%)	Crude HRs (95% CI)
Total	2249	268 (12)	
Age, y			
75–79 (Ref)	1033	96 (9)	1.00
80–84	952	123 (13)	1.45 (1.11, 1.89)
≥85	264	49 (19)	2.20 (1.56, 3.10)
Education <sup>a</sup>			
Less than high school	223	34 (15)	1.60 (1.05, 2.43)
High school graduate	585	65 (11)	1.04 (0.73, 1.47)
Some college or trade school	865	106 (12)	1.14 (0.83, 1.56)
College graduate (Ref)	573	61 (11)	1.00
Race/ethnicity <sup>b</sup>			
White (Ref)	2009	237 (12)	1.00
Black	91	13 (13)	1.11 (0.62, 1.99)
Hispanic	67	7 (10)	0.93 (0.44, 1.97)
Asian/Pacific Islander	34	2 (6)	0.50 (0.13, 2.02)
Other	42	10 (24)	2.17 (1.15, 4.08)
Marital status <sup>c</sup>			
Married or living with partner (Ref)	962	101 (11)	1.00
Other	1119	167 (13)	1.27 (.99, 1.62)
Depression			
Yes	515	80 (16)	1.68 (1.30, 2.17)
No (Ref)	1734	188 (11)	1.00
Stroke			
Yes	157	34 (22)	2.32 (1.63, 3.29)
No (Ref)	2092	234 (11)	1.00
Myocardial infarction			
Yes	274	31 (11)	1.04 (0.72, 1.51)
No (Ref)	1975	237 (12)	1.00
Hypertension			
Yes	1717	204 (12)	1.25 (0.95, 1.65)
No (Ref)	532	64 (12)	1.00
Diabetes			
Yes	228	42 (18)	1.93 (1.40, 2.66)
No (Ref)	2021	226 (11)	1.00
Parkinson's disease			
Yes	41	7 (17)	1.72 (0.82, 3.59)
No (Ref)	2208	261 (12)	1.00
Hormone use			
Yes	1201	135 (11)	0.86 (0.68, 1.09)
No (Ref)	1048	133 (13)	1.00
TICS–m score			
≤27	587	126 (21)	2.85 (2.24, 3.62)
>27 (Ref)	1662	142 (9)	1.00

Note. HR = hazard ratio; CI = confidence interval; TICS–m = Telephone Interview for Cognitive Status–modified.

<sup>a</sup>Information was missing for 3 participants.

<sup>b</sup>Information was missing for 6 participants.

<sup>c</sup>Information was missing for 1 participant.

were 0.60 (95% CI=0.45, 0.79) for the family subscale and 0.73 (95% CI=0.56, 0.95) for the friends subscale. After adjusting for hormone use and TICS–m scores at baseline, we calculated the fully adjusted HR for dementia on the LSNS-6 total to be 0.74 (95% CI=0.57, 0.97). With the lower subscale cutoff score (0–5) as the referent, the fully adjusted HRs for dementia were 0.64 (95% CI=0.48, 0.85) for the family subscale and 0.85 (95% CI=0.66, 1.10) for the friends subscale.

We used less-than-weekly contact as the referent and found that daily contact reduced the adjusted HRs for dementia by almost half (0.57; 95% CI=0.38, 0.87). Satisfaction with amount of contact did not reduce the risk of dementia, with an adjusted HR of 0.70 (95% CI=0.48, 1.01).

We tested the interactions between the stratified TICS–m scores and the LSNS-6 scores at baseline and found no significant interaction ( $P=0.41$ ), indicating that cognitive status did not alter the influence of social network at baseline. However, low cognitive scores (i.e., ≤27) on the TICS–m in 2001 were associated with development of dementia and with low scores on the social network scale in subsequent years. The mean TICS–m score was 30.1 (SD=6.1). The mean TICS–m score for women without dementia as of last contact was 30.8 (SD=5.7), compared with 24.9 (SD=6.0) for the women who had developed dementia to date ( $P<.001$ ). Of the women who scored 0 to 11 on the social network scale, 203 (45%) also scored 27 or below on the TICS–m, compared with 498 (28%) of participants with a social network score of 12 to 30 ( $P<.001$ ).

We explored a possible interaction between hormone use and social networks and found no significant difference in social network scores between hormone users and nonusers. Finally, we examined a possible interaction between marital status and the LSNS-6. Marital status was associated with LSNS-6 scores but did not diminish the association between the LSNS-6 and dementia.

## DISCUSSION

In this large cohort of elderly women who did not have dementia in 2001, larger social networks were associated with lower risk of

**TABLE 2—Association of Social Network, Frequency of Contact, and Satisfaction With Contact With Incidence of Dementia Among Elderly Women: Southern California, 2002–2005**

	Study Population, No.	Participants Who Developed Dementia, No. (%)	Crude HR (95% CI)	Model 1, Adjusted HR (95% CI) <sup>a</sup>	Model 2, Adjusted HR (95% CI) <sup>b</sup>
LSNS-6 score					
0–11 (Ref)	456	80 (18)	1.00	1.00	1.00
12–30	1793	188 (10)	0.53 (0.41, 0.69)	0.63 (0.48, 0.83)	0.74 (0.57, 0.97)
LSNS family subscale					
0–5 (Ref)	396	71 (18)	1.00	1.00	1.00
6–15	1853	197 (11)	0.52 (0.40, 0.69)	0.60 (0.45, 0.79)	0.64 (0.48, 0.85)
LSNS friends subscale					
0–5 (Ref)	579	91 (16)	1.00	1.00	1.00
6–15	1670	177 (11)	0.65 (0.50, 0.83)	0.73 (0.56, 0.95)	0.85 (0.66, 1.10)
Contact frequency <sup>c</sup>					
< 1 time/wk (Ref)	157	27 (17)	1.00	1.00	1.00
1–2 times/wk	332	40 (12)	0.66 (0.40, 1.07)	0.66 (0.40, 1.10)	0.58 (0.36, 0.93)
3–6 times/wk	613	73 (12)	0.64 (0.41, 1.00)	0.66 (0.42, 1.04)	0.66 (0.42, 1.02)
1 time/d	1144	127 (11)	0.61 (0.40, 0.92)	0.59 (0.38, 0.91)	0.57 (0.38, 0.87)
Satisfied with contact <sup>d</sup>					
No (Ref)	209	36 (17)	1.00	1.00	1.00
Yes	2035	230 (11)	0.60 (0.42, 0.85)	0.72 (0.51, 1.02)	0.70 (0.48, 1.01)

Note. HR = hazard ratio; CI = confidence interval; LSNS-6 = abbreviated Lubben Social Network Scale.

<sup>a</sup>Model 1 adjusted for age, education, and selected health conditions (depression, stroke, myocardial infarction, hypertension, diabetes, and Parkinson's disease).

<sup>b</sup>Model 2 adjusted for age, education, selected health conditions, hormone use, and the baseline score for the Telephone Interview for Cognitive Status–modified.

<sup>c</sup>Information was missing for 3 participants.

<sup>d</sup>Information was missing for 5 participants.

dementia over a 4-year follow-up. Validated measures of social networks and cognitive status provided evidence that a supportive social network had a beneficial association with cognitive function and risk for dementia. Our results suggested that a large social network, as measured by the LSNS-6, and daily social contact were associated with a substantially lower risk of dementia. This lower risk of dementia persisted even after adjustment for age, education, depression, and other health conditions.

These findings suggest that social networks may facilitate access to health care and healthy behaviors and thereby indirectly reduce or forestall brain pathology and other conditions that affect cognition. Still, establishing a direct link between social network and cognitive functioning and dementia is necessarily complex.<sup>42</sup> Some evidence suggests a possible association between neuroendocrine measures of stress and dementia.<sup>43</sup> If social engagement or isolation affects neuroendocrine function,

then a biological link to aspects of cognition may exist. Data from studies of older animals also point to a possible physiological link whereby “environmental enrichment and stimulation increase capillary formation, synaptogenesis, and neurogenesis.”<sup>44(p685)</sup> These preliminary data suggest that social support networks may act on aspects of neuronal functioning. In addition, social networks have been associated with stress and depression known to affect brain function.

Bennett et al. measured Alzheimer disease brain pathology, cognitive function, and social networks in 89 elderly people without known dementia who underwent annual clinical assessments and who had brain autopsies at the time of death.<sup>45</sup> Lower cognitive function was associated with severe pathology, but social network size reduced the association between cognition and pathology, and despite having severe disease pathology, those with larger social networks retained better cognitive

function. Our results are consistent with previous longitudinal studies in which lack of social ties was associated with increased risk of cognitive decline<sup>13</sup> and incident dementia.<sup>14</sup> Although emotional support was found to be a significant predictor of cognition in another study,<sup>16</sup> no association between social ties and dementia was found. This difference in results may be attributable to the latter study's relatively younger, healthier sample population and the use of different cognitive tests.

A critical question for future research is whether synthetic social networks can be created to either augment or substitute for naturally occurring networks, thereby lowering health risk factors for those with more limited social networks. Hogan et al. reviewed 100 social support intervention studies.<sup>46</sup> Although the authors noted mixed results regarding the efficacy of support interventions, they offered suggestions for improving future studies. Recent studies also offer promise for how specific knowledge of social support networks among older adults might be incorporated into geriatric practice.<sup>47–50</sup>

### Limitations

Our study's limitations included a lack of minority participants; small numbers did not permit useful comparisons among groups. By design, our sample was limited to women who were 78 years and older, belonged to a health maintenance organization, and were selected by their use of hormone replacement therapy. However, no relationship between hormone use and dementia or hormone use and social network score was found. Moreover, although these elderly women may have appeared to be more socially connected than their counterparts who were not members of a health maintenance organization, their score on the LSNS-6 were comparable to those of a mostly female elderly population in a large European study.<sup>33</sup> Further, the results might have been different had men been included. Previous studies suggested that men and women perceive and report on social networks and support differently<sup>51</sup> and that the nature of social ties has a variable influence on cognition in men.<sup>6</sup> Engagement with friends was found to be associated with lower rates of cognitive decline for women but not for men.<sup>6</sup>

Selection and recall biases of the participants posed an additional problem. Cognitive decline and early dementia may result in a reduction of interaction and social network support or may imply a failure to recall and report offered support. We diminished this problem by analyzing women who were dementia free at the start of follow-up, but some cognitive impairment cannot be ruled out.

Another limitation was attrition from death and dropping out. Complete death data for 2005 were not available from the California Death Index. However, when we applied the same risk analyses to this population through 2004 only, the results of the social network scores and dementia did not change. Further, we conducted analyses to estimate competing risks of dementia from other hazards, and results were similar. The existence of dementia among women who died or dropped out was unknown. Dropouts had a lower mean TICS–m score (29.4; SD=6.4) than did those who remained in the study (31.5; SD=5.3). Thirty-six percent of women who dropped out and 22% of women who continued scored 27 or lower on the TICS–m ( $P<.001$ ). Women who dropped out also scored lower on the LSNS-6, with a mean score of 15.8 (SD=5.1); women who continued had a mean score of 16.8 (SD=5.4). Twenty-three percent of women who dropped out and 17% who continued scored between 0 and 11 on the LSNS-6 ( $P<.001$ ).

We found no significant differences in contact frequency or satisfaction with contact between groups or in depression and all other health conditions. Dropouts were more likely to be older and non-White and to have less education. The possibility that death with undetected dementia or the differential dropout rate of participants with low social support biased our estimate of dementia risk cannot be excluded. The risk of dementia and its association with social networks, however, is likely to be higher in light of the trend that women who dropped out, as a group, scored lower on the TICS–m and the LSNS-6 measures.

## Conclusions

Strengths of our study included a large sample size and large number of incident dementia cases over 4 years of follow-up. We used validated methods of dementia classification

and social network measures. Our results provide additional longitudinal evidence that large social networks have a protective association with cognition and the development of dementia among elderly women. Future studies are needed to determine what specific aspects of social networks are associated with dementia risk and maintenance of cognitive health. ■

## About the Authors

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## Contributors

V.C. Crooks originated the study and supervised all aspects of its implementation. J. Lubben assisted in the study methods, analyses, and interpretation of findings. D.B. Petitti assisted in the design and analyses. D. Little supported the implementation of the study and contributed to data collection. V. Chui assisted with data management and completed the analyses. All authors participated in the preparation of the article and made significant contributions to the conception and design of the study, analysis and interpretation of the data, and review of article drafts.

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## Human Participant Protection

This study was reviewed and approved by the Kaiser Permanente Southern California institutional review board for the protection of human participants.

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