ABSTRACT

Objectives To evaluate whether mid-life marital status is related to cognitive function in later life.

Design Prospective population based study with an average follow-up of 21 years.

Setting Kuopio and Joensuu regions in eastern Finland.

Participants Participants were derived from random, population based samples previously investigated in 1972, 1977, 1982, or 1987; 1449 individuals (73%), aged 65-79, underwent re-examination in 1998.

Main outcome measures Alzheimer’s disease and mild cognitive impairment.

Results People cohabiting with a partner in mid-life (mean age 50.4) were less likely than all other categories (single, separated, or widowed) to show cognitive impairment later in life at ages 65-79. Those widowed or divorced in mid-life and still so at follow-up had three times the risk compared with married or cohabiting people. Those widowed both at mid-life and later life had an odds ratio of 7.67 (1.6 to 40.0) for Alzheimer’s disease compared with married or cohabiting people. The highest increased risk for Alzheimer’s disease was in carriers of the apolipoprotein E ε4 allele who lost their partner before mid-life and were still widowed or divorced at follow-up. The progressive entering of several adjustment variables from mid-life did not alter these associations.

Conclusions Living in a relationship with a partner might imply cognitive and social challenges that have a protective effect against cognitive impairment later in life, consistent with the brain reserve hypothesis. The specific increased risk for widowed and divorced people compared with single people indicates that other factors are needed to explain parts of the results. A sociogenetic disease model might explain the dramatic increase in risk of Alzheimer’s disease for widowed apolipoprotein E ε4 carriers.

INTRODUCTION

As life expectancy is increasing in various regions of the world, dementia is becoming a growing public health concern. In 2005 an estimated 25 million people had dementia, and the number is expected to double every 20 years in the future, reaching 81.1 million in 2040.1 In the Western world the prevalence has been estimated as around 15% among 80 year olds and 25% for those over 85,2 12 with Alzheimer’s disease being the most common diagnosis.2 Besides the consequences for the patients and their families, patients might require intensive care, especially in the more advanced stages of the disease. The healthcare costs for people with cognitive impairments in the United Kingdom are estimated to rise from £5.4bn in 2002 to £16.7bn in 2031.3 There is no known cure, although knowledge about biological mechanisms and behavioural risk factors is steadily accumulating.

Several studies have suggested an association between lifestyle and cognitive decline. Education,4-8 physical activity,9 10 mentally demanding work,11 higher managerial positions,12 and various leisure and intellectual activities13-15 have all been reported to predict a more favourable cognitive status later in life. A rich social network has also been linked to a lower risk of cognitive impairment and dementia.16-17 Follow-up times in these studies ranged from three to five years, with only one exception,16 meaning that people were typically already in their later years (>65) at baseline measurements. The possibility of “reverse causation” is illustrated by the findings of the only study on social factors with a longer (27.5 years) follow-up.16 That study found an association between social engagement and dementia in later life, whereas no such association was found for mid-life data. The possibility of subclinical dementia before any association established through studies with short follow-up is further strengthened by findings of abnormal cognitive function five years8 to eight years16 before a diagnosis of dementia. One study reported subclinical decline up to nine years before a diagnosis, with an acceleration three years before—that is, all within typical follow-up times of previous prospective studies on social factors and cognitive decline.

Many studies have reported that living as a couple and the quality of the relationship are both positively correlated with health and longevity.21 22 Few prospective studies, however, have specifically examined the association between marital status and the risk of dementia.23-27 The categorisation of marital status differed somewhat between these studies, but all but one27...
found an increased risk of dementia from living without a partner, either as single, \textsuperscript{23,25} single or divorced, \textsuperscript{26} or unmarried.\textsuperscript{24} Follow-up times in these studies range from three years\textsuperscript{25} to 10 at the most.\textsuperscript{24}

We specifically evaluated the relevance of marital status in mid-life, with adjustments for various other variables that were also measured at baseline, for cognitive status later in life.

**METHODS**

**Study design**

We used a population based design with participants from two regions in eastern Finland. Participants were examined in mid-life (mean (SD) age 50.4 (6.0) years) and then again around 21 years later. The main variables were marital status (married/cohabiting, single, divorced, or widowed) measured at mid-life and follow-up and additional diagnostic measures of cognitive impairment (mild cognitive impairment, Alzheimer’s disease, and other forms of dementia) at follow-up. By combining marital status at both times, we created several categories of marital transition (such as married at both times, married in mid-life and widowed later in life, etc). We then related mid-life marital status and transitions in marital status from mid-life to later life to cognitive status later in life. We adjusted the estimations of these associations for several other variables from the mid-life measurements. Finally, we investigated if carriers of the apolipoprotein E e4 allele, the most important currently known genetic risk factor for Alzheimer’s disease, were especially at risk for cognitive impairment later in life if they also lived alone after losing their partner.

**Participants**

This research was part of the cardiovascular risk factors, aging and dementia (CAIDE) study. The participants of the CAIDE study comprised a random sample of 2000 survivors from four separate population samples, originally investigated in 1972, 1977, 1982, or 1987. These investigations assessed cardiovascular risk factors within the North Karelia Project and the FINMONICA study. The four original samples were randomly drawn from the population register of two regions in eastern Finland and comprised 30,078 participants aged 30-59. Each original sample was stratified so that there were at least 250 participants from each sex and from each of the three 10 year age intervals. The participation rate in the baseline investigations was 82-90%.

By the end of 1997, 2000 randomly selected survivors, all from or nearby the cities of Kuopio and Joensuu and aged 65-79, were invited for re-examination during the following year. The mean follow-up time was 20.9 years (SD 4.9). Altogether 1449 (73%), then aged 65-80 (mean age 71.3, SD 4.9), were able to or agreed to participate. This sample constitutes the database for the present study, together with the data from the baseline measurements and register linked data from later in life for the 551 non-participants. Figure 1 shows details of the flow of participants.

There were few differences between the flow of participants and non-participants at mid-life.\textsuperscript{26} Non-participants were somewhat older and less educated, had higher cholesterol concentration, blood pressure, and body mass index, and fewer of them did office or service work. Fewer were married or cohabiting (73.5% v 79.9% for participants).

**Mid-life measurements**

The survey methods used during baseline (mid-life) examinations complied with the WHO MONICA protocol, described in more detail elsewhere.\textsuperscript{25} In brief, the baseline survey included a self administered questionnaire on health behaviour, health status, signs of depression, and medical history. Trained nurses checked the questionnaires to ensure that they were fully completed and understood. Participants’ blood pressure, height, and weight were measured, and body mass index calculated. A venous blood specimen was taken to determine serum cholesterol concentration. A questionnaire classified marital status into four categories: married/cohabiting, separated/divorced, single, or widowed.

**Later life measurements**

During the re-examination in 1998, the survey methods followed those applied in the previous surveys in all aspects. In addition, we identified participants’ apolipoprotein genotype by using polymerase chain reaction and Hhal digestion, as described by Tsukamoto.
Cognitive status was assessed with a three step protocol for the diagnosis of dementia: a screening phase, a clinical phase, and a differential diagnostic phase. The 294 participants who scored 24 or less on the mini-mental state examination (MMSE) were referred for further examinations, including thorough neurological, cardiovascular, and neuropsychological assessments. Those with possible dementia, based on these assessments and as judged by an expert board, were referred to the differential diagnostic phase, including magnetic resonance imaging of the brain. In the final step, the review board re-analysed all data from the three phases before establishing the final diagnosis. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), criteria in 57 participants. The diagnostic criteria for Alzheimer’s disease was fulfilled in 48 of these according to criteria from the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association. All patients with a diagnosis of Alzheimer’s disease showed generalised or medial temporal lobe atrophy, or both, without relevant vascular pathology, as revealed by magnetic resonance imaging. Mild cognitive impairment was diagnosed in 82, according to a procedure previously described, derived from the criteria advised by the Mayo Clinic Alzheimer’s disease research centre. The main criteria were objective impairment below 1.5 SD of the age appropriate mean in either memory or one other area of cognitive functioning, along with memory complaints. Marital status was determined by the same procedure as in mid-life.

We collected data on diagnoses of dementia in the 551 non-participants from local hospitals and healthcare centres. The total number of cases increased to 113 (5.9% of the population) when we took these diagnoses into account. As we lacked information on diagnosis procedures, apolipoprotein, and late marital status, we used this group only for reference to cross validate main results.

**Statistical analysis**

Directly relating the four categories of marital status in mid-life to all categories of cognitive impairment resulted in unacceptably low numbers of participants in some of the cells. Because we were interested in whether the reason for living without a partner would make any difference, in addition to collapsing the three non-cohabiting categories into one—that is, comparing cohabitants with non-cohabitants in mid-life—we used three categories: living with a partner, single/divorced, or widowed. This choice was based on theoretical and statistical considerations. Being widowed is the result of a traumatic, imposed, and involuntary marital transition that distinguishes it from the other two non-cohabitating categories (single and divorced). This assumption was reinforced by preliminary analyses that revealed a linear relation with the risk of cognitive impairment (measured by χ² and logistic regressions) so that widowed people had the highest risk, single and separated or divorced people emerged as a middle category, and married people had the lowest risk (see table 2).

By combining marital status in mid-life and later life, 13 theoretically possible categories of marital transition emerged (table 1). Based on these, we classified marital transition as cohabiting with a partner on both occasions, cohabiting with a partner in mid-life but not in later life, and living without a partner on both occasions. (The fourth category, living without a partner in mid-life but cohabiting in later life contained too few people to be used in calculations and it was not possible to combine it with any other category.) We performed separate calculations with this variable treated either as nominal or ordinal. The ordinal assumption was that each of the three categories should be associated with different amounts of time spent in a cohabiting partner relation from mid-life onwards. Cognitive impairment was first treated as an “all inclusive” variable, comprising the 139 participants with a diagnosis of mild cognitive impairment or any kind of dementia. For more detailed analysis, we analysed mild cognitive impairment and Alzheimer’s disease separately. In each of the three analyses, the 1270 participants without any signs of cognitive impairment served as reference. In alternative calculations we entered cognitive function as ordinal, assuming that mild cognitive impairment represents a milder form of impairment than Alzheimer’s disease.

We used logistic regression to analyse the association between marital status and cognitive status later in life. Apart from adjustment for variables of most obvious relevance to predict dementia, such as age, apolipoprotein E ε4 status, and education, we decided to adjust only for those variables for which we had data for all, or almost all, of the 1449 participants who were screened for dementia. Among these, we identified several variables related to marital status (table 2). Two further variables were selected for their contribution to the regression model after adjustments—namely, blood pressure and residence area. In the case of multicollinearity, we chose the variable that contributed most in the regression model. Because of this criterion, we chose age at follow-up instead of follow-up time and systolic blood pressure rather than diastolic blood pressure.

**Table 1** Marital status transitions* between mid-life and follow-up

<table>
<thead>
<tr>
<th>Mid-life marital status</th>
<th>Married/cohabitant</th>
<th>Single</th>
<th>Separated/divorced</th>
<th>Widowed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married/cohabitant</td>
<td>809</td>
<td>59</td>
<td>279</td>
<td>1147</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>9</td>
<td>100</td>
<td>1</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>9</td>
<td>0</td>
<td>50</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>Widowed</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>105</td>
<td>111</td>
</tr>
<tr>
<td>Total</td>
<td>813</td>
<td>100</td>
<td>111</td>
<td>389</td>
<td>1432</td>
</tr>
</tbody>
</table>

*Four main transition categories: cohabiting with partner on both occasions (n=809), cohabiting with partner in mid-life but not in later life (n=338), living without partner on both occasions (n=262), and living without partner in mid-life but cohabiting in later life (n=23); omitted in calculations because of too few participants to combine with dementia categories separately and inadequacy of combining it with any other category. Data on both mid-life and late marital status were missing for 17.
Table 2 | Differences between marital status groups at mid-life in participants from Kuopio or Joensuu, Finland. Figures are means (SD) unless stated otherwise

<table>
<thead>
<tr>
<th>Variables:</th>
<th>Married (n=1270)</th>
<th>Single (n=166)</th>
<th>Separated/divorced (n=97)</th>
<th>Widowed (n=174)</th>
<th>Total</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%) who participated in follow-up</td>
<td>1157 (74.1)</td>
<td>112 (67.5)</td>
<td>63 (64.9)</td>
<td>116 (66.7)</td>
<td>1999</td>
<td>0.021</td>
</tr>
<tr>
<td>No (%) with cognitive impairment at follow-up</td>
<td>98 (8.6)</td>
<td>12 (11.1)</td>
<td>7 (11.7)</td>
<td>22 (20.4)</td>
<td>1409</td>
<td>0.001</td>
</tr>
<tr>
<td>No (%) of ApoE e4 carriers (one or two alleles)</td>
<td>413 (36.6)</td>
<td>34 (31.2)</td>
<td>20 (32.3)</td>
<td>32 (29.4)</td>
<td>1407</td>
<td>0.31</td>
</tr>
<tr>
<td>Age at follow-up (years)</td>
<td>71.2 (4.0)</td>
<td>71.2 (4.0)</td>
<td>70.4 (6.1)</td>
<td>72.9 (4.1)</td>
<td>1447</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>21.2 (4.8)</td>
<td>20.7 (4.7)</td>
<td>19.9 (4.8)</td>
<td>18.6 (5.1)</td>
<td>1447</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No (%) of women</td>
<td>652 (56.4)</td>
<td>91 (81.3)</td>
<td>46 (73.0)</td>
<td>111 (95.7)</td>
<td>1448</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mid-life variables:
- Education (years) | 8.6 (3.47) | 9.1 (3.42) | 8.2 (2.87) | 7.5 (3.31) | 1427 | 0.003 |
- Age (years) | 50.0 (5.9) | 50.5 (5.9) | 50.5 (5.8) | 54.3 (5.2) | 1447 | <0.001 |
- Total cholesterol (mmol/l) | 6.7 (1.18) | 6.9 (1.28) | 6.5 (1.36) | 7.0 (1.27) | 1448 | 0.03 |
- Systolic blood pressure (mm/Hg) | 145 (19.5) | 145 (23.0) | 141 (20.4) | 145 (22.8) | 1448 | 0.50 |
- Diastolic blood pressure (mm/Hg) | 90 (10.8) | 89 (11.5) | 87 (13.3) | 88 (11.2) | 1448 | 0.27 |
- BMI | 26.7 (3.6) | 25.7 (4.7) | 26.4 (3.6) | 26.5 (3.8) | 1436 | 0.04 |
- Occupational physical activity† | 1.96 (0.91) | 1.81 (0.90) | 2.02 (0.91) | 1.76 (0.84) | 1436 | 0.04 |
- No (%) of smokers | 530 (45.8) | 35 (31.3) | 25 (39.7) | 31 (26.7) | 1447 | <0.001 |
- No (%) of office workers | 515 (44.5) | 64 (57.1) | 28 (44.4) | 45 (38.8) | 1448 | 0.04 |
- No (%) from Kuopio | 530 (45.8) | 60 (53.6) | 32 (50.8) | 55 (47.4) | 1448 | 0.73 |
- Signs of depression‡ | 6.8 (2.3) | 7.2 (2.4) | 7.6 (2.7) | 7.1 (2.4) | 1403 | 0.07 |

All the analyses were adjusted for age (at re-examination), education, sex, and apolipoprotein E e4 status (e4 carriers v non-carriers). In the next step we additionally adjusted for mid-life systolic blood pressure, cholesterol concentration, body mass index, smoking, occupation (farming/forestry as reference), region of residence, occupational physical activity, and signs of depression.

Each step of adjustment added significantly to explain the total variance in the regression model. Because progressive adjustments did not significantly change the association studied, we have presented only the final models, including all the adjustments.

RESULTS
Mid-life marital status: sociodemographic and clinical characteristics

Table 2 shows sociodemographic and clinical characteristics of the participants according to categories of mid-life marital status. Most widowed participants were women and somewhat older at follow-up; single people were somewhat more educated and more had office jobs; more married participants were smokers.

We adjusted for all these variables. We found no differences in vascular risk factors in mid-life. Cognitive impairment later in life was more common among participants living without a partner in mid-life. The largest discrepancy was found for widowed people with more than twice as many cases as expected.

Mid-life marital status and cognitive impairment in later life
People living without a partner at mid-life had around twice the risk of developing cognitive impairment in later life compared with people living with a partner, even after all adjustments (table 3). Independent calculations for mild cognitive impairment and Alzheimer’s disease, with consequential loss of statistical power, showed similar odds ratios, significant for mild cognitive impairment and of borderline significance for Alzheimer’s disease. When the model treated single or divorced and widowed people separately, and in addition independently relating them to mild cognitive impairment and Alzheimer’s disease, significance was lost for the single or divorced category. The high odds ratios for those widowed in mid-life was 2.76 (P=0.002) for broad cognitive impairment and 3.30 (P=0.001) for mild cognitive impairment (table 3).

We cross checked the results for mid-life marital status and confirmed them with ordinal logistic regression (cognitive function as normal-mild cognitive impairment-Alzheimer’s disease). When calculated this...
Table 3 | Association between mid-life marital status and cognitive impairment later in life.*

<table>
<thead>
<tr>
<th></th>
<th>Cognitive impairment (n=131/1303)</th>
<th>Mild cognitive impairment (n=78/1250)</th>
<th>Alzheimer’s disease (n=44/1216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without partner</td>
<td>2.09 (1.3 to 3.4)</td>
<td>2.14 (1.2 to 3.8)</td>
<td>2.06 (0.9 to 4.7)</td>
</tr>
<tr>
<td>Widowed</td>
<td>2.76 (1.5 to 5.2)</td>
<td>3.30 (1.6 to 6.9)</td>
<td>2.52 (0.8 to 7.7)</td>
</tr>
<tr>
<td>Single/divorced</td>
<td>1.56 (0.9 to 2.8)</td>
<td>1.50 (0.7 to 3.4)</td>
<td>1.78 (0.7 to 4.9)</td>
</tr>
</tbody>
</table>

*Adjusted for age at follow-up, years of education, ApoE e4, sex, BMI, systolic blood pressure, cholesterol, occupation, physical activity at work, region of residence, smoking, and signs of depression at mid-life. Some participants without data on all adjustment variables were excluded from this analysis.

Table 4 | Association between marital transition and cognitive impairment later in life. Figures are odds ratios (95% confidence intervals)*

<table>
<thead>
<tr>
<th></th>
<th>Cognitive impairment (n=129/1274)</th>
<th>Mild cognitive impairment (n=78/1223)</th>
<th>Alzheimer’s disease (n=42/1187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partner in mid-life, but not at follow-up†</td>
<td>1.60 (1.0 to 2.7)</td>
<td>1.75 (0.9 to 3.3)</td>
<td>1.60 (0.7 to 3.8)</td>
</tr>
<tr>
<td>Without partner in mid-life and follow-up†</td>
<td>2.89 (1.7 to 5.0)</td>
<td>3.17 (1.7 to 6.0)</td>
<td>2.83 (1.1 to 7.4)</td>
</tr>
<tr>
<td>Ordinal assumption‡</td>
<td>1.70 (1.3 to 2.2)</td>
<td>1.78 (1.3 to 2.5)</td>
<td>1.67 (1.0 to 2.7)</td>
</tr>
</tbody>
</table>

*Adjusted for age at follow-up, years of education, ApoE e4, sex, BMI, systolic blood pressure, cholesterol, occupation, physical activity at work, region of residence, smoking, and signs of depression at mid-life. The ordinal logistic analysis confirmed that entering cognitive status as an ordinal outcome reduced the sample size further from 551 to 488. As apolipoprotein data, later life data, and adjustments reduced the sample size further from 551 to 488. Table 3 shows the corresponding odds ratio for apolipoprotein E e4 carriers who had been widowed or divorced both at mid-life and later life, the odds ratio for Alzheimer’s disease was 7.67 (1.6 to 40.0, P=0.01) compared with those living with a partner on both occasions.

Differences within the non-cohabitant group

To focus separately on those who were single both at mid-life and follow-up, we performed logistic regression with those living with a partner on both occasions as reference. After adjustment, the odds ratio for cognitive impairment (dementia plus mild cognitive impairment) was 1.94 (0.9 to 4.4) for being single on both occasions. An analogous separate logistic regression on people who were widowed or divorced on both occasions yielded odds ratios of 3.53 (1.7 to 7.4) and 2.74 (0.96 to 6.4), respectively.

Sex differences

The uneven distribution between men and women in this age group and in the different non-cohabitant categories (see table 2) allowed for sex comparisons only for the broadest categories of non-cohabitants in relation to general cognitive impairment. Compared with cohabitants, the odds ratio for mid-life non-cohabitants was 1.87 (1.1 to 3.3) for women and 2.59 (1.0 to 6.7) for men (fully adjusted model). For those who were cohabiting in mid-life and not cohabiting in late-life, the odds ratio was 2.12 (0.7 to 5.7) for women and 2.38 (1.0 to 5.7) for men. For non-cohabiting both in mid-life and future life the odds ratio was 2.38 (1.2 to 4.7) for women and 3.56 (1.3 to 9.5) for men.

Non-participants

Odds ratios were similar for non-participants when we calculated them in the same way but without adjustment for apolipoprotein status. When we dichotomised participants into living with or without a partner in mid-life, the odds ratio for dementia was 1.85 (0.9 to 4.0) for those who lived without a partner in mid-life. When we compared those either divorced or widowed with those who were still married in mid-life, the corresponding odds ratio was 2.22 (0.9 to 5.4). The non-participant group, however, was rather small and adjustments reduced the sample size further from 551 to 488. As apolipoprotein data, late-life data, and specific diagnoses of Alzheimer’s disease were all
missing for non-participants, we could not cross validate other results.

**DISCUSSION**

There is a substantial and independent association between marital status in mid-life and cognitive function later in life. People without a partner had twice the risk of developing cognitive impairment and Alzheimer’s disease compared with people living with a partner. The risk for cognitive impairment was even higher for those without a partner both at mid-life and later life. The long follow-up period, the large and representative population based sample, adjustment for several possible confounders, robust significances, similar odds ratios for Alzheimer’s disease and mild cognitive impairment, alternative calculations with consistent results, and similar odds ratios for non-participants all contribute to the credibility of our results. The increase in risk was significant for men and women, with slightly higher odds ratios for men. Because of small numbers in these sub-analyses, we cannot draw safe conclusions about possible sex differences.

**Beyond the brain reserve hypothesis**

As various forms of intellectual and social activity have been reported to protect against dementia,14-17 our observed associations with marital status might not seem surprising. The decreased risk of cognitive impairment later in life might reflect the effects of a high level of social and intellectual stimulation inherent in a couple relationship, consistent with the brain reserve hypothesis18-20 and indirectly with results from animal experiments on enriched environments.21-22

A more careful analysis of the results tells a somewhat different story. If the amount of time living without a partner was the critical risk factor, single life, here defined as never married, would obviously be associated with the highest risk. The odds ratios indicate, however, that despite having lived part of their lives in a couple relationship, the incidence of cognitive impairment was considerably higher in widowed people. Some specific risk factor seems to be associated with staying widowed, which to a lesser degree, if at all, is associated with other reasons for living without a partner.

Associations with cognitive impairment have been reported for several risk factors that might also be related to marital status, such as hypertension, high cholesterol concentration, obesity, physical inactivity, and smoking.23-25 For depression there are almost no prospective studies with long follow-up and the evidence is more controversial.26 We adjusted for all these factors without noticeably affecting the odds ratios.

**Reverse causation**

In the Honolulu-Asia aging study, Saczynski et al included marital status (married v unmarried) in a social engagement index together with four other social activity variables.27 They performed regression analysis with adequate adjustments in relation to this combined index, rather than to marital status specifically, but did not significantly predict dementia an average of 27.5 years later. In later life, however, 4.7 years before the first screening for dementia, the index was predictive of dementia. The authors discuss the predictive difference between mid-life and later life social engagement as possible evidence of reverse causation. There is evidence for subclinical effects up to nine years before a diagnosis of dementia,28-30 but with baseline measurements on average 21 years before diagnosis and a mean age of participants of 50.4 years (SD 6.0), reverse causation seems unlikely in our study, at least for mid-life marital status.

For the marital transition variable, however, including marital status in both mid-life and later life, reverse causation is possible, at least for those who lost their partners after mid-life. Odds ratios for this group were somewhat lower than for non-cohabitants at mid-life and considerably lower than those who lived without a partner both at mid-life and later life. These results seem to go against reverse causation as an explanation for those who lost their partner after mid-life. Saczynski et al measured social engagement in a wider sense, with marital status as only one of several indicators.31 The discrepancy in results could be explained by the various other social activities included in their social engagement index, some of which might be more sensitive to the effects of reverse causation than later life marital status.

**Marital status confounders**

In addressing a study by Verghese et al,32 Coyle argued that the protective effect of mental activities could be an epiphenomenon.33 By referring to the nun studies by Snowdon et al,34 Coyle made the point that non-random groups might initially differ in several ways besides the one being studied and that such differences might lie behind both the variable being studied and the risk of cognitive impairment later in life. This kind of initial bias, when people assign themselves to different groups, is a problem in non-experimental designs, including epidemiological research on dementia.35 So even if reverse causation seems improbable in our study because of mid-life baseline measurements and
Being widowed from mid-life onwards was associated with the highest risk of cognitive impairment later in life with a highly significant odds ratio of 7.67 for Alzheimer’s disease.

Reversing causation, a major methodological problem in these studies, means that most studies are based on data collected later in life and have short follow-up periods. The tentative “sociogenetic” link indicated by our results could mean that psychosocial trauma of sufficient size and with long-term negative emotional and disruptive immunological consequences could increase the risk of an existing genetic vulnerability leading to the development of the corresponding disease. For an apolipoprotein E4 carrier, Alzheimer’s disease might be the more probable disease outcome in such a scenario. Evidence for immunological dysfunctions as a risk factor for Alzheimer’s disease seems to add to the credibility of such a speculation.

Implications for prevention
For those who look for interventions to prevent the development of Alzheimer’s disease, the results should be encouraging. If the proposed sociogenetic model proved valid, supportive intervention for individuals who have lost a partner might be a promising strategy in preventive health care. Our results also add to a growing body of evidence for the general importance of social factors in sustaining healthy brain functioning. A couple relationship might offer unique opportunities in this regard, perhaps not only through social and cognitive stimulation.

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