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Marital status and risk of dementia: a nationwide population-based prospective study

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Abstract

Objectives: To examine the association between marital status and dementia, and also whether this may differ by gender.

Design: Prospective population-based study with follow-up time of up to ten years.

Setting: Swedish national register-based study.

Participants: 1 996 296 individuals, aged 50-70 years, without prior dementia diagnosis at baseline. Dementia was identified using the Swedish National Patient Register and the Cause of Death Register.

Outcome measures: The influence of marital status on dementia was analysed using Cox proportional hazards models, step-wise adjusted for multiple covariates (Model 1: adjusted for age as time scale, and gender; and Model 2: additional adjusted for having adult children, education, income, and prior cardiovascular disease).

Results: During follow-up, 16 772 individuals were identified as demented. Cox regression showed each non-married subcategory to be associated with significantly higher risk of dementia than the group of married, with the highest risk observed among people who are single or divorced (hazard ratios 1.65 to 1.71, fully adjusted model). Analyses stratified by gender showed gender differences when adjusting for age only, with indications of unmarried men (singles and divorced) having higher relative risk compared to unmarried women. However, in the fully adjusted model these gender differences were no longer observed. The estimated hazard ratio for widowed where smaller, although statistically significant, indicating an increased risk for this group in the full sample results, but separate analysis by gender attenuated the association for widowed men, after which it was no longer statistically significant.

Conclusion: Although more research is needed to understand the underlying mechanism by which marital status is associated with dementia, health care providers should be particularly attentive to unmarried elderly and provide them with extra support to reduce social isolation and loneliness.

Keywords: marital status, dementia, prospective, nationwide study, register-based study

Strengths and limitations of this study

- The study was based on data from various Swedish registers, and includes the entire Swedish population, with a follow-up period of up to ten year.
- We found that marriage was beneficially associated with dementia, and all non-married subcategories were associated with higher incidence of dementia.
- The association between marital status and incident dementia was evident for both men and women to a similar degree. However, the estimated increase in risk observed for widows was relatively small and statistically insignificant in some stratified sub-samples.
- The population register used in this study have been reported to have high specificity of detecting dementia, but lower sensitivity (e.g. missing cases of dementia).
- Further studies are required to explore more thoroughly the mechanism underlying this association.

Introduction

Due to global aging, the number of people suffering from age-related diseases, such as dementia, will rise substantially and will certainly be one of the most serious challenges of the 21st century.[1] Therefore, it is increasingly important to identifying attributes/groups at risk and factors that can reduce the risk of dementia.

A growing body of literature indicates that aspects of social relationship are associated with incident dementia.[2 3] One aspect that has drawn increasing interest in recent years concerns the effect of marriage on dementia. Among the few studies explicitly investigating this, the majority have found marriage/cohabitation to have a beneficial effect on dementia risk,[3-7] although this is not consistently reported.[8] Moreover, there is conflicting evidence as to whether all or just some unmarried states are related to dementia risk; whereas some have found an association only for those who are single,[3 5] others have reported an association for both single and divorced people,[4] and still others have found increased risk only among widows/widowers.[6 7]

Many researchers have revealed gender differences in the effect of marital status on various physical health outcomes, generally showing men to benefit more from marriage than women do.[9 10] For example, one study reported a 250% higher mortality rate for unmarried compared to married men, and a 50% higher mortality rate for unmarried compared to married women.[11] Furthermore, a longitudinal study of a Finnish cohort[6] found non-cohabitant men to have higher odds ratios of experiencing a cognitive impairment later in life compared to non-cohabitant women. Although it is reasonable to believe that there may be gender differences in dementia risk among the single, divorced and widowed, to the best of our knowledge this has not been explicitly examined before.

The aim of this study was to evaluate the association between marital status and dementia, while controlling for potential confounders. We also assessed whether there were

differences in risk of dementia across the marital status categories. Finally, since there may be gender differences in the association between marital status and dementia, we separated the analyses for men and women. Our study uses data from an extensive national registry that encompasses the entire Swedish population. This data have the added benefit of having a long follow-up period (up to 10 years).

Method

Data

The study was based on data from the Linnaeus database comprising of longitudinal nationwide data with linked records from various registers, including data from the National Patient Register and the Cause of Death Register.[12] The National Patient Register covers all in-patient hospitalization in Sweden, and includes the entire Swedish population. It has been shown to demonstrate a high level of completeness, with a predictive value of about 85-95% for most diagnoses.[13] The Cause of Death Register covers all deceased persons since 1952 who were residents in Sweden at time of death, and includes official death certificates. The register has low under-reporting; for example, in 2000 the non-reporting rate was less than 0.58% of all deaths.[14]

Both registers are based on diagnoses according to the International Classification of Diseases (ICD). The Linnaeus database also includes yearly records of individual and family characteristics, e.g., marital status, income, education, and number of children, for all Swedish citizens from various registers held by Statistics Sweden.

Study population and end-point

The study population was defined as the total Swedish population aged 50-70, according to the Swedish population register from 1997, amounting to 2 022 295 individuals. A total of 25 999 persons were excluded due to having been diagnosed with dementia before

baseline (2 860), emigration or death at the enter (13), or having missing data on baseline characteristics (23 126). Hence, the final study population comprised of 1 996 296 individuals.

The study populations were followed from January 1, 1997, to December 31, 2006, through the linked registers in the Linnaeus database. Follow-up ended at the first of the following: date of dementia diagnosis, death, or end of the study period.

Marital status

Information on marital status was obtained from Statistics Sweden. Marital status in 1997 was selected as current marital status, and was classified into four categories: (1) married, (2) single, (3) divorced, or (4) widowed.

Ascertainment of dementia

Dementia was identified using both the National Patient Register and the Cause of Death Register. In previous studies, combining the two registers has been found to enhance the detection rate;[15 16] hence, this approach was used in the present study. The registers have been reported to have high specificity for detecting dementia, but lower sensitivity (e.g., missing dementia cases). Of note is that, despite the moderate sensitivities, data on dementia from these register have been considered to be overall accurate, specific, and feasible for conducting dementia cohort studies.[15 16]

To identify a dementia diagnosis, the following codes from the ICD-10 were used: F00.0-9, G30.0-9, F01.0-9, F02.0-8, F03, F03.9 G31.9, and R54.9. Both diagnoses/death causes listed as primary or secondary (e.g. the first 7 diagnoses/death causes in the register) were considered. In the analyses, all dementia groups were combined to define dementia (yes/no). If there were multiple reports of dementia diagnosis, we recorded only the date of the first of admission.

Covariates

Analyses were adjusted for variables measuring attributes that have been shown to be potential confounders at baseline in previous literature: age, having adult children, education (classified as low [≤ 9 years], intermediate [10-12 years], and high [≥ 13 years]). We further adjust for taxable income and previous history of cardiovascular diseases during the years 1987-1996. Cardiovascular diseases were defined as the first hospitalization caused by coronary heart disease, stroke, or heart failure, and were coded according to the ICD-9 codes (410-414, 428, 430-438, and 440-448).

Statistical analyses

Multivariate adjusted Cox's proportional hazard regression models, with age as the time scale, were used to analyse the association between marital status and incident dementia. When age is used as the time scale, it implies that age is automatically adjusted for. In Model 1, age (time scale) and gender were adjusted for. In Model 2, additionally adjustments were made for having adult children, education, income, and prior cardiovascular disease. Finally, to examine possible gender differences in the association between marital status and incident dementia, we repeated all analyses separately for men and women. Time to event was calculated from the time of enrolment on the study until the time of dementia diagnosis, being lost to follow-up, death, or date of final follow-up, whichever event came first.

The results are presented as hazard ratios (HR) with a 95% confidence interval (CI). Statistical analyses were performed using the stcox package in the Stata statistical software package (STATA 12).

Results

Background characteristics of the study population, by marital status and gender, are listed in Table 1. The mean age of the individuals at entry was 58.8 years, and the proportion of women was 50.3%. Among both men and women, those who were widowed were older

and had lower education as well as more often a history of prior cardiovascular diseases in comparison to the other marital status categories. Married men had the highest income and single women the highest education. Mean follow-up time was 6.2 years for individuals who were diagnosed as demented (defined either through diagnoses or death causes) and 8.7 years for those who remained dementia-free.

During the follow-up time, observations of dementia amounted to 16 772 individuals. The mean age of dementia onset differed depending on marital status: 71.5 years for married women, 71.6 years for married men, 69.5 years for single women, 69.1 years for single men, 70.1 years for divorced women, 69.0 years for divorced men, 73.0 years for widowed women, and 72.5 years for widowed men.

Association between marital status and dementia

We evaluated the impact of marital status on incident dementia using Cox proportional regression analysis with age as time scale, and step-wise adjusted for multiple covariates (Table 2). In the basic model (Model 1), each non-married subcategory was significantly associated with higher risk of dementia relative to the married sample, with the highest risk observed for the divorced group (hazard ratio 1.71, 95% confidence interval 1.64 to 1.78) and singles (1.68, 1.60 to 1.76). Additional adjustment for having adult children, education, income, and prior cardiovascular diseases (Model 2), led to similar results, with the highest risk for divorced and singles (divorced; 1.67, 1.61 to 1.74, and single; 1.65, 1.56 to 1.75). The estimated hazard ratios for widows (Model 1; 1.07, 1.02 to 1.13, and Model 2; 1.10, 1.04 to 1.15) where significantly lower in comparison with the other non-married groups, but still showed a small and statistically significant increase in risk compared to married individuals.

Association between marital status and dementia by gender

To examine possible gender differences in the association between marital status and dementia, we re-ran all models stratified by gender (Tables 3 and 4). There was a statistically

significant gender difference between men and women in Model 1, with non-married men – especially divorced men – showing a higher risk compared to non-married women. However, this gender difference was no longer evident when adjustment was made for the extended set of confounders in Model 2. Thus, the gender differences shown in the estimates of Model 1 seem to be partially driven by gender differences in socioeconomic status (e.g. education and income) and other confounders; particularly the estimated hazard ratios for divorced men in Model 1 decreases after adjustment for the extended set of confounders.

Although, separated analysis by gender did not alter the results for divorced and singles in the fully adjusted model, it attenuated the association for widowed men, after which it was no longer statistically significant. Hence, the gender specific estimates suggest an increased risk of dementia among both single and divorced men and women, and a substantially smaller, though still significantly, higher risk for widowed women.

Discussion

In this large nationwide population-based study, encompassing nearly two million individuals, it was found that people who are single or divorced have an increased risk of incident dementia, as compared to married individuals. A smaller but significant increase risk was also observed for widows/widowers. The estimated protective effect of marriage persisted even after adjustment for several potential confounders (age, having adult children, education, income, and prior cardiovascular diseases). The association between marital status and dementia varies by gender when only age was adjusted for, with higher risk among divorced and single men. But after accounted for socioeconomic factors, the initially observed gender differences were no longer significant. However, for widows the association attenuated and was no longer statistically significant for men.

Our findings are consistent with previous results showing a beneficial effect of marriage on dementia,[3-7] suggesting that this association is highly robust. This study also helps clarifying previous inconsistent findings about difference in risk across subcategories of non-married group. In contrast to our study, two recent studies[6 7] reported no increased risk for single and divorced. The inconsistencies may be due to these studies small sample sizes and limited statistic power to be able to detect possible differences. In this study, with the largest sample size in the literature reported so far, we found an increased risk for all subcategories, with the highest hazard ratios for divorced and single.

Our study also adds evidence that unmarried (single or divorced) status is associated with dementia to a similar magnitude for men and women (fully adjusted model). Since this study, to the best of our knowledge, is the first to explicitly examine this, no direct comparison can be made between our estimates and those from previous studies. However, previous work on risk of cognitive impairment has shown non-cohabiting men to be at greater risk compared to non-cohabiting women.[6] Similar to their results, we found a relatively higher risk for unmarried men. However, after adjustment for socioeconomic and other factors, the hazard ratios were still slightly higher among men than women, but now with overlapping confidence intervals and no statistically significant difference in risk. Thus, socioeconomic and other factors seems to account for some of the initially observed difference in the association between marital status and dementia in men and women, respectively.

Potential mechanisms

While the specific mechanisms by which marital status influences the risk of dementia remain to be understood, several possible alternatives – not necessarily mutually exclusive – have been hypothesized. First, a close relationship may be one of the best sources of cognitive stimulation, and may thereby be linked to the hypothesis of cognitive reserve. A high cognitive reserve is suggested to provide the individual with resilience against

neuropathological damage to the brain, such as dementia.[17] In addition, a person who lives with someone may be less lonely and receive more social support, which is found to reduce psychological distress, including anxiety and depression.[18] Individuals with more social support are also provided with better resources for coping with stressors, and are less prone to assess stressors as threatening.[19] Moreover, widowhood and divorce are regarded as severe stressful events, whereas marriage may serve as a buffer against negative consequences of adverse life events.[20] Although we were not able to adjust for these variables in the current study, however, Sundström et al[7] adjusted for both depressive symptoms and stressful life events but still observed a beneficial effect of marriage on incident dementia.

Other proposed mechanisms concern the selection effect into marriage (which states that healthier people are more likely to both get and stay married) and the protection effect of marriage (which states that marriage provides increased social support and income, while also reducing unhealthy behaviours).[21] In our study, which consisted of upper middle-aged and elderly adults, we could not examine selection effects into marriage since most people marry long before these ages, but we could adjust for socioeconomic and health aspects (e.g. education, income, and cardiovascular diseases) at baseline. However, adjustment for these confounders did not notably influence the observed beneficial effect of marriage. Socioeconomic status at baseline may partially reflect effects of marital status, but aspects such as low income may also reflect early onset of cognitive impairment. Although the tests of gender differences in estimated risks by marital status are somewhat sensitive to model specification, the overall conclusion of higher relative risks for non-married individuals seemed not to be dependent on whether or not socioeconomic indicators are adjusted for.

Limitations

Our study has several possible limitations that need to be addressed. One is the use of a dementia diagnosis provided by the national registers. Although previous studies using the

Swedish National Patient and the Cause of Death Registers have reported very high specificity of dementia identification but lower sensitivity,[15 16] there seems to be no difference in disease detection based on gender or education.[15] Furthermore, systematic differences by marital status in underreporting and misclassification (sensitivity and specificity) may potentially be a source of biased estimates. In the absence of firm evidence, one can only speculate on this point. If anything, one would expect married people to be subject to examination at an earlier stage of dementia, e.g. at the initiative of their partners, than those who are non-married.[22] Our estimates of higher risks among the non-married would then be biased downwards and represent an underestimation of differences in risk between married and unmarried individuals.

Another aspect of the empirical framework is that events occurring after baseline are not adjusted for because of the potential risk of reversed causality.[23] For this reason, differentiation depending on transition in or out of marital status during follow-up, such as remarriage, was not performed. Remarriage and divorce may in fact be outcomes that are partially determined by health status. However, robustness checks considering marital transition did not affect our main results.

Conclusions and future work

In conclusion, non-married individuals, irrespective of marital status subcategory, appear to be at increased risk of dementia, with the highest risk observed for divorced and single. Although the results suggest a gender difference in risk of dementia, the association between marital status and incident dementia does not seem to differ in magnitude between single and divorced men and women. Further studies are required to develop better understanding of the mechanisms and pathways through which marriage plays a protective role regarding dementia. Until then, the results of this study suggest that health care providers

should be especially attentive to elderly people who are unmarried, and accordingly provide them with extra support to reduce their social isolation and loneliness.

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Competing interests: The authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The Linnaeus database has been approved by the Regional Ethical Committee at Umeå University DNR 07-142Ö.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

Table 2. Cox proportional hazard regression estimates of the association between marital status and dementia.

	Model 1[a]	Model 2[b]
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Marital Status		
Married	Reference	Reference
Single	1.68 (1.60 to 1.76)***	1.65 (1.56 to 1.75)***
Divorce	1.71 (1.64 to 1.78)***	1.67 (1.61 to 1.74)***
Widowed	1.07 (1.02 to 1.13)**	1.10 (1.04 to 1.15)***
Gender		
Men	Reference	Reference
Women	0.79 (0.77 to 0.82)***	0.77 (0.74 to 0.79)***
Education level:		
≤ 9		Reference
10 – 12 years		1.05 (1.01 to 1.08)**
≥ 13		0.89 (0.85 to 0.94)***
Taxable income		0.85 (0.85 to 0.86)***
Having children		
No		Reference
Yes		1.03 (0.98 to 1.08)
Prior cardiovascular disease		
No		Reference
Yes		1.58 (1.51 to 1.65)***

Note. [a]adjusted for age as survival time; [b]adjusted for age as survival time, gender, education, taxable income, having children, and prior vascular diseases. *$p < .05$, **$p < .01$,***$p < .001$

Table 3. Cox proportional hazard regression estimates of the association between marital status and dementia for men.

	Model 1[a]	Model 2[b]
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Marital Status		
Married	Reference	Reference
Single	1.75 (1.65 to 1.86)***	1.71 (1.59 to 1.85)***
Divorce	1.82 (1.72 to 1.93)***	1.73 (1.64 to 1.83)***
Widowed	1.08 (0.97 to 1.19)	1.07 (0.96 to 1.18)
Education level:		
≤ 9		Reference
10 – 12 years		1.09 (1.04 to 1.14)***
≥ 13		0.91 (0.85 to 0.98)**
Taxable income		0.86 (0.85 to 0.87)***
Having children		
No		Reference
Yes		1.07 (0.99 to 1.14)
Prior cardiovascular disease		
No		Reference
Yes		1.52 (1.44 to 1.61)***

Note. [a]adjusted for age as survival time; [b]adjusted for age as survival time, gender, education, taxable income, having children, and prior vascular diseases. *$p < .05$, **$p < .01$,***$p < .001$

Table 4. Cox proportional hazard regression estimates of the association between marital status and dementia for women.

	Model 1[a]	Model 2[b]
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Marital Status		
Married	Reference	Reference
Single	1.56 (1.44 to 1.69)***	1.61 (1.47 to 1.76)***
Divorce	1.59 (1.50 to 1.68)***	1.62 (1.53 to 1.72)***
Widowed	1.04 (0.98 to 1.11)	1.09 (1.03 to 1.16)**
Education level		
≤ 9		Reference
10 – 12 years		1.01 (0.96 to 1.06)
≥ 13		0.88 (0.82 to 0.95)***
Taxable income		0.85 (0.84 to 0.85)***
Having children		
No		Reference
Yes		0.99 (0.92 to 1.06)
Prior cardiovascular disease		
No		Reference
Yes		1.69 (1.58 to 1.82)***

Note. [a]adjusted for age as survival time; [b]adjusted for age as survival time, gender, education, taxable income, having children, and prior vascular diseases. *$p < .05$, **$p < .01$,***$p < .001$

Table 1. Baseline Characteristics of the Study Sample by Marital Status. Values are numbers (percentages) unless stated otherwise.

Characteristic	Men				Women			
	Married (n=669 441)	Single (n=137 278)	Divorced (n=155 286)	Widowed (n=25 859)	Married (n=642 140)	Single (n=85 902)	Divorced (n=180 248)	Widowed (n=100 153)
Mean (SD) age, years	58.8 (6.1)	57.3 (6.0)	58.0 (5.8)	62.8 (5.8)	58.7 (6.1)	57.4 (6.1)	58.0 (5.9)	63.3 (5.6)
Education level:								
≤ 9	39.6%	54.3%	41.5%	50.6%	41.0%	37.7%	35.7%	54.4%
10 – 12 years	40.6%	34.1%	42.7%	36.3%	39.3%	38.0%	44.1%	34.0%
≥ 13	19.8%	11.6%	15.8%	13.1%	19.7%	24.3%	20.2%	11.6%
Mean taxable income, SEK	6.55	5.66	5.93	6.37	5.97	5.83	5.93	5.94
Having children	91.5%	30.2%	90.0%	85.6%	91.5%	43.6%	91.5%	88.3%
Prior cardiovascular disease	8.3%	6.9%	9.0%	12.6%	3.4%	3.1%	4.1%	5.8%

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Marital status and risk of dementia: a nationwide population-based prospective study

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Abstract

Objectives: To examine the association between marital status and dementia in a cohort of young-old (50-64) and middle-old (65-74) adults, and also whether this may differ by gender.

Design: Prospective population-based study with follow-up time of up to ten years.

Setting: Swedish national register-based study.

Participants: 2 288 489 individuals, aged 50-74 years, without prior dementia diagnosis at baseline. Dementia was identified using the Swedish National Patient Register and the Cause of Death Register.

Outcome measures: The influence of marital status on dementia was analysed using Cox proportional hazards models, step-wise adjusted for multiple covariates (Model 1: adjusted for age and gender; and Model 2: additionally adjusted for having adult children, education, income, and prior cardiovascular disease).

Results: During follow-up, 31 572 individuals in the study were identified as demented. Cox regression showed each non-married subcategory to be associated with significantly higher risk of dementia than the married group, with the highest risk observed among people in the young-old age group, especially among those who were divorced or single (hazard ratios 1.79 vs 1.71, fully adjusted model). Analyses stratified by gender showed gender differences in the young-old group, with indications of divorced men having higher relative risk compared to divorced women (hazard ratios 2.1 vs 1.7, only-age adjusted model). However, in the fully adjusted model, these differences were attenuated and there was no longer any significant difference between male and female subjects.

Conclusion: Our results suggest that those living alone as non-marrieds may be at risk for both early- and late-onset dementia. Although more research is needed to understand the

underlying mechanism by which marital status is associated with dementia, this suggests that social relationships should be taken seriously as a risk factor for dementia and that social-based interventions may provide an opportunity to reduce the overall dementia risk.

Strengths and limitations of this study

- The study was based on data from various Swedish registers and includes the entire Swedish population, aged 50-74 at baseline, with a follow-up period of up to ten years.
- Due to the large sample size, we were able to estimate risk for subcategories of non-married status and to divide the sample into gender and age groups (50-64 and 65-74).
- Limitations concern the use of dementia identification from national registers, which may underreport cases of dementia.
- Time in respective marital statuses was unavailable, which may have affected the results.

Introduction

Due to global increase in life expectancy, the number of people suffering from age-related diseases such as dementia will rise substantially and represents one of the most serious challenges of the 21st century.[1] Therefore, it is increasingly important to identify attributes and groups at increased risk and factors that can reduce the risk of dementia.

A growing body of literature indicates that aspects of social relationships are associated with the incidence of dementia.[2 3] One aspect that has drawn increasing interest in recent years concerns the effect of marriage on dementia. Among the few studies explicitly investigating this, the majority have found marriage/cohabitation to have a beneficial effect on dementia risk,[3-7] although this is not consistently reported.[8] Moreover, there is conflicting evidence as to whether all or just some unmarried states are related to dementia risk; whereas some studies have found an association only for those who are single,[3 5] others have reported an association for both single and divorced people,[4] while still others have found increased risk of dementia only among widows/widowers.[6 7]

Many researchers have highlighted gender differences in the effect of marital status on various physical health outcomes, generally showing men to benefit more from marriage than women do.[9 10] For example, one study reported a 250% higher mortality rate for unmarried compared to married men, and a 50% higher mortality rate for unmarried compared to married women.[11] Furthermore, a longitudinal study of a Finnish cohort[6] found non-cohabitant men to demonstrate higher ratios of experiencing a cognitive impairment later in life compared to non-cohabitant women. Although it is reasonable to believe that there may be gender differences in dementia risk among the single, divorced, and widowed, to the best of our knowledge this has not been explicitly examined before.

The aim of this study was to evaluate the association between marital status and dementia while controlling for potential confounders. We also assessed whether there were

differences in risk of dementia across the marital status categories. Moreover, in order to investigate whether there are differences between early- and late onset of dementia, we separate the analysis into two age groups: young-old (50-64) and middle-old (65-74). Finally, since there may be gender differences in the association between marital status and dementia, we separated the analyses for men and women. Our study uses data from an extensive national registry that encompasses the entire Swedish population. This data also has the added benefit of having a long follow-up period (up to 10 years).

Method

Data

The study was based on data from the Linnaeus database comprising longitudinal nationwide data with linked records from various registers, including data from the National Patient Register and the Cause of Death Register.[12] The National Patient Register covers all in-patient hospitalizations in Sweden and includes the entire Swedish population. The National Patient Register has been shown to demonstrate a high level of completeness, with a predictive value of about 85-95% for most diagnoses.[13] The Cause of Death Register covers all deceased persons since 1952 who were residents of Sweden at time of death, and includes official death certificates. The register offers low under-reporting; for example, in 2000 the non-reporting rate was less than 0.58% of all deaths.[14] Both registers are based on diagnoses according to the International Classification of Diseases (ICD).

The Linnaeus database also includes yearly records of individual and family characteristics, e.g., marital status, income, education, and number of children, for all Swedish citizens from various registers held by Statistics Sweden.

Study population and end-point

The study population was defined as the total Swedish population aged 50-74 (born 1923-1947) registered as residents in Sweden as of December 31, 1997, amounting to 2 326 013 individuals. A total of 37 524 persons were excluded due to having been diagnosed with dementia prior to baseline (5 459), emigration or death at entry (13), or having missing data on any of the baseline characteristics (32 052). Hence, the final study population was comprised of 2 288 489 individuals.

The study populations were followed to December 31, 2006, through the linked registers in the Linnaeus database. Follow-up ended at the first of the following: date of dementia diagnosis, death, or end of the study period.

Marital status

Information on marital status was obtained from Statistics Sweden. Marital status in 1997 was selected as the current marital status, and was classified into four categories: (1) married, (2) single, (3) divorced, or (4) widowed.

Ascertainment of dementia

Dementia was identified using both the National Patient Register and the Cause of Death Register. In previous studies, combining the two registers has been found to enhance the detection rate;[15 16] hence, this approach was used in the present study. The registers have been reported to have high specificity for detecting dementia, but lower sensitivity (e.g., missing dementia cases). Of note is that, despite the moderate sensitivities, data on dementia from these registers have been considered to be overall accurate, specific, and feasible for conducting dementia cohort studies.[15 16]

To identify a dementia diagnosis, the following codes from the ICD-10 were used: F00.0-9, F01.0-9, F02.0-8, F03, F03.9, G30.0-9, G31.9, and R54.9. Both diagnoses/death causes listed as primary or secondary (e.g. the first 7 diagnoses/death causes in the register) were considered. In the analyses, all dementia groups were combined to define dementia

(yes/no). If there were multiple reports of dementia diagnosis, we recorded only the date of the first admission.

Covariates

Analyses were adjusted for variables measuring attributes that have been shown in previous literature to be potential confounders: age, having adult children, education (classified as low [≤ 9 years], intermediate [10-12 years], and high [≥ 13 years]). We further adjusted for taxable income and previous history of cardiovascular diseases during the years 1987-1996. Cardiovascular diseases were defined as the first hospitalization caused by coronary heart disease, stroke, or heart failure, and were coded according to the ICD-9 codes (410-414, 428, 430-438, and 440-448).

Statistical analyses

Multivariate adjusted Cox's proportional hazard regression models were used to analyse the association between marital status and incidence of dementia. In Model 1, we adjusted for age and gender. In Model 2, additional adjustments were made for having adult children, education, income, and prior cardiovascular disease. Finally, to examine possible age and gender differences in the association between marital status and incidence of dementia, we repeated all analyses separately for the two age cohorts (50-64, 65-75) and for the two genders. Time to event was calculated from the time of enrolment in the study until the time of dementia diagnosis, of being lost to follow-up, death, or date of final follow-up, whichever event came first.

The results are presented as hazard ratios (HR) with a 95% confidence interval (CI). Statistical analyses were performed using SPSS Statistics version 22.

Results

Background characteristics of the study population, by marital status and gender, are listed in Table 1. The mean age of the individuals at entry was 60.5 (±7.3) years, and the proportion of women was 51.0%. Among both men and women, those who were widowed were older and had lower levels of education as well as more often a history of prior cardiovascular diseases in comparison to the other marital status categories. Married men had the highest income and single women the highest education. Mean follow-up time was 6.0 years for individuals who were diagnosed as demented (defined either through diagnoses or death causes) and 8.6 years for those who remained dementia-free.

Table 1. Baseline characteristics of the study sample by marital Status. Values are numbers (percentages) unless stated otherwise.

Characteristic	Men				Women			
	Married (n=762 962)	Single (n=150 974)	Divorced (n=167 763)	Widowed (n=38 674)	Married (n=721 792)	Single (n=96 115)	Divorced (n=197 482)	Widowed (n=152 727)
Mean (SD) age, years	60.5 (7.3)	58.7 (7.2)	59.1 (6.7)	66.0 (6.7)	60.2 (7.2)	59.0 (7.4)	59.3 (6.9)	66.5 (6.4)
Education level:								
≤ 9	41.3%	56.5%	42.7%	53.8%	43.7%	39.3%	37.7%	59.5%
10 – 12 years	39.7%	32.6%	41.9%	34.2%	38.0%	37.1%	43.2%	30.9%
≥ 13	19.0%	10.9%	15.4%	12.0%	18.4%	23.6%	19.1%	9.6%
Mean taxable income, SEK	6.62	5.77	6.01	6.62	6.02	5.94	6.00	6.21
Having children	91.1%	28.3%	89.8%	84.8%	91.2%	41.1%	91.3%	87.8%

Prior cardiovascular disease	9.8%	7.8%	10.0%	15.7%	4.1%	3.7%	4.8%	7.7%

During the follow-up period, observations of dementia were found in 31 572 individuals. The mean age of dementia onset differed depending on marital status: 74.9 years for married women, 74.8 years for married men, 73.3 years for single women, 72.2 years for single men, 73.5 years for divorced women, 72.0 years for divorced men, 76.6 years for widowed women, and 76.0 years for widowed men.

To assess whether marital status influence the risk of dementia differently before and after the age of 65, the population was divided into two age groups: young-old (50-64) and middle-old (65-74). The mean age at baseline of those in the young-old group (n=1 538 360) was 56.1 (±4.3) years while the mean age in the middle-old group (n=750 129) was 69.4 (±2.9) years. During follow-up, dementia diagnoses were recorded for 5 850 individuals in the young-old group and for 25 722 individuals in the middle-old group.

Association between marital status and dementia

We evaluated the impact of marital status on incidence of dementia for the two age groups using Cox proportional regression analysis and adjusted for multiple covariates. In the young-old group and for the basic model (Model 1, adjusted for age and gender), each non-married subcategory was significantly associated with a higher risk of dementia relative to the married sample, with the highest risk observed for the divorced group (hazard ratio 2.05, 95% confidence interval 1.91 to 2.21) and the single group (1.91, 1.79 to 2.03). A slightly lower, but still significant, increased risk was observed among the widowed 1.38 (1.23 to 1.54). Also in the middle-old group (Model 1), each non-married subcategory showed significantly higher risk of dementia compared to the married group. Similar to the young-old group, in the middle-old group the highest risk was observed for those who were divorced (1.42, 1.37 to 1.47), followed by singles (1.26, 1.21 to 1.32), and widowed (1.12, 1.08 to 1.16).

After additional adjustment for having adult children, education, income, and prior cardiovascular diseases (Model 2), the hazard ratios were attenuated but continued to be

statistically significant for all non-married categories. As can be seen in Table 2, the hazard ratios were somewhat higher in the young-old, compared to the middle-old, group, and were particularly high for those divorced (hazard ratios: young-old; 1.79 and middle-old; 1.42), followed by singles (young-old; 1.71 and middle-old; 1.23). Thus, although a significant association was noted for both age groups, this association was more pronounced for the young-old group. The estimated hazard ratios for widows (young-old; 1.28 and middle-old; 1.12) where significantly lower in comparison with the other non-married groups in both age groups, but still showed a statistically significant increase in risk compared to married individuals. Note that the overall average risk is very low for the younger cohort (3.8 promille) and almost ten times higher for the older cohort (3.4 percent).

Table 2. Cox proportional hazard regression estimates of the association between marital status and dementia for young-old respectively middle-old group (fully adjusted model).

	Young-old	Middle-old
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Age	1.17 (1.16 to 1.18)***	1.18 (1.17-1.19)***
Gender		
Men	Reference	Reference
Women	0.79 (0.75 to 0.83)***	0.88 (0.86 to 0.91)***
Having adult children		
No	Reference	Reference
Yes	0.89 (0.83 to 0.97)**	0.96 (0.92 to 0.99)*
Education level:		
≤ 9	Reference	Reference

10 – 12 years	0.96 (0.91 to 1.02)	0.96 (0.93 to 0.98)**
≥ 13	0.77 (0.70 to 0.83)***	0.84 (0.81 to 0.88)***
Taxable income	0.89 (0.88 to 0.90)***	0.97 (0.94 to 0.99)**
Prior cardiovascular disease		
No	Reference	Reference
Yes	1.89 (1.74 to 2.04)***	1.50 (1.45 to 1.55)***
Marital Status		
Married	Reference	Reference
Single	1.71 (1.57 to 1.87)***	1.23 (1.17 to 1.29)***
Divorce	1.79 (1.68 to 1.90)***	1.42 (1.36 to 1.47)***
Widowed	1.28 (1.14 to 1.43)***	1.12 (1.08 to 1.19)***

Note. *$p < .05$, **$p \leq .01$, ***$p \leq .001$

Association between marital status and dementia by gender

To examine possible gender differences in the association between marital status and dementia, we re-ran all models stratified by gender (Table 3). There was a statistically significant gender difference between men and women in the young-old group, with divorced men showing a higher risk compared to divorced women (men; 2.10 and women; 1.70). However, this gender difference was considerably reduced after adjustment was made for the extended set of confounders in Model 2 (men; 1.89 and women: 1.68). Thus, the gender differences shown in the estimates of Model 1 seem to be partially driven by gender differences in socioeconomic status (e.g. education and income) and other confounders.

Table 3. Cox proportional hazard regression estimates of the association between marital status and dementia for young-old respectively middle-old group by gender.

	Model 1[a]		Model 2[b]	
	Men	Women	Men	Women
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Young-old				
Married	Reference	Reference	Reference	Reference
Single	2.12 (1.94 to 2.32)***	1.96 (1.73 to 2.21)***	1.72 (1.54 to 1.94)***	1.76 (1.54 to 2.02)***
Divorce	2.10 (1.93 to 2.28)***	1.70 (1.55 to 1.86)***	1.89 (1.74 to 2.06)***	1.68 (1.53 to 1.85)***
Widowed	1.43 (1.15 to 1.77)***	1.31 (1.15 to 1.50)***	1.33 (1.07 to 1.66)**	1.24 (1.09 to 1.42)***
Middle-old				
Married	Reference	Reference	Reference	Reference
Single	1.32 (1.25 to 1.40)***	1.18 (1.10 to 1.27)***	1.29 (1.20 to 1.38)***	1.16 (1.07 to 1.25)***
Divorce	1.48 (1.40 to 1.56)***	1.36 (1.29 to 1.43)***	1.47 (1.39 to 1.55)***	1.36 (1.29 to 1.43)***

Widowed	1.10 (1.03 to 1.18)**	1.11 (1.06 to 1.15)***	1.10 (1.02 to 1.17)**	1.10 (1.05 to 1.41)***

Note. [a]adjusted for age (model 1), [b]adjusted for age, gender, education, taxable income, having children, and prior vascular diseases (model 2). *$p < .05$, **$p < .01$,***$p < .001$

Even though there were also higher risk ratios for men than women, in the middle-old group (see Table 3) these differences were not significantly different between the two genders and were further reduced in the fully adjusted model.

To summarize, the gender-specific estimates suggest an increased risk of dementia for non-married men and women, particularly among the young-old, and a substantially smaller, though still statistically significant, risk for widowed men and women.

Discussion

In this large, nationwide population-based study encompassing approximately two million individuals, it was found that non-married people have an increased risk of incidence of dementia as compared to married individuals. The estimated protective effect of marriage persisted even after adjustment for several potential confounders. When only age was adjusted for, the benefit of marriage was stronger for men, particularly relative to being divorced, but after adjustment for socioeconomic and other factors, the initial gender difference was significantly reduced. In addition, marital status was related to both early- and late-onset dementia, with a slightly higher risk for early-onset dementia, which has not been previously shown.

Our findings are consistent with previous study results showing a beneficial effect of marriage on dementia,[3-7] suggesting that this association is highly robust. But in contrast to these studies which are based on smaller data sets, we find that the risk of dementia was observed across all-non-married categories. Of note is that two recent studies[6 7], one by our research group[7], suggest a particular high risk among the widowed, but in the current study with its large sample, we found a lower risk for widowhood compared to the other non-married categories. The lower estimate for the widowed might be related to the fact that

dementia develops over a long period and that the duration of widowhood in the present study might be of insufficient length for many people to be fully manifested in dementia during that time. This is in comparison to, for example, those living as single, which is a state that a person might have been in for a long time and perhaps even for his or her entire adult life. Hence, although we found a significantly increased risk of dementia for those widowed compared to their married counterparts the risk ratios may been somewhat underestimated.

Our study also adds evidence that all non-married statuses are associated with dementia for both men and women. Since this study, to the best of our knowledge, is the first to explicitly examine this phenomenon, no direct comparison can be made between our estimates and those from previous studies. However, previous work on the risks of cognitive impairment has shown non-cohabiting men to be at greater risk compared to non-cohabiting women.[6] Similar to those results, we found a relatively higher risk of cognitive impairment for divorced men, but after adjusting for socioeconomic and other factors, the hazard ratios were still slightly higher among men than women, but now with overlapping confidence intervals and no longer statistically significant difference in risk. Thus, socioeconomic and other factors seem to account for some of the initially observed differences by gender in the association between marital status and dementia.

Potential mechanisms

While the specific mechanisms by which marital status influences the risk of dementia remain to be understood, several possible options – not necessarily mutually exclusive – have been hypothesized. First, a close relationship may be one of the best sources of cognitive stimulation, and may thereby be linked to the hypothesis of cognitive reserve. A high cognitive reserve is suggested to provide the individual with resilience against neuropathological damage to the brain, such as occurs in dementia.[17] In addition, a person

who lives with someone may be less lonely and receive more social support, which is found to reduce psychological distress, including anxiety and depression.[18] Individuals with more social support also have access to better resources for coping with stressors and are less prone to assess stressors as threatening.[19] Moreover, being widowed or divorced are regarded as severely stressful events, whereas marriage may serve as a buffer against the negative consequences of adverse life events.[20] Although we were not able to adjust for these variables in the current study, Sundström et al[7] adjusted for both depressive symptoms and stressful life events but still observed a beneficial effect of marriage on incidence of dementia.

Other proposed mechanisms concern the selection effect of marriage (which states that healthier people are more likely to both get and stay married) and the protection effect of marriage (which states that marriage provides increased social support and income, while also reducing unhealthy behaviours).[21] In our study, which consisted of upper middle-aged and elderly adults, we could not examine selection effects of marriage since most people marry long before the ages of the individuals we studied, but we could adjust for socioeconomic and health aspects (e.g. education, income, and cardiovascular diseases) at baseline. However, adjusting for these confounders did not notably influence the observed beneficial effect of marriage. Socioeconomic status at baseline may partially reflect the effects of marital status, but aspects such as low income may also reflect early onset of cognitive impairment. Although the tests of gender differences in estimated risks by marital status are somewhat sensitive to model specification, the overall conclusion of higher relative risks for non-married individuals seemed not to be dependent on whether or not socioeconomic indicators were adjusted for.

Limitations

Our study has several possible limitations that need to be addressed. One is the use of a dementia diagnosis as provided by the national registers. Although previous studies using

the Swedish National Patient and the Cause of Death Registers have reported very high specificity of dementia identification but lower sensitivity,[15 16] there seems to be no difference in disease detection based on gender or education.[15] In addition, there are many types of dementia, with Alzheimer´s disease and vascular dementia as the two major forms, but there is also a considerable overlap between different subtypes of dementia, and distinguishing among them can be difficult, especially at an early stage and for early-onset dementia.

Furthermore, systematic differences by marital status in underreporting and misclassification (sensitivity and specificity) may potentially be a source of biased estimates. In the absence of firm evidence, one can only speculate on this point. If anything, one would expect married people to be subject to examination at an earlier stage of dementia, e.g. at the initiative of their partners, than those who are non-married.[22] Our estimates of higher risks among the non-married would then be biased downward and represent an underestimation of differences in risk between married and unmarried individuals.

Another limiting aspect of the empirical framework is that events occurring after baseline are not adjusted for because of the potential risk of reversed causality.[23] For this reason, differentiation depending on transition in or out of marital status during follow-up, such as remarriage, was not performed. Remarriage and divorce may in fact be outcomes that are partially determined by health status. However, robustness checks considering marital transition did not affect our main results.

Conclusions and future work

In conclusion, non-married individuals, regardless of marital status subcategory, appear to be at increased risk of both early- and late-onset dementia. Although the results initially suggested a gender difference in the risk of dementia, the association between marital status and incidence of dementia does not seem to differ significantly between men and

women in the fully adjusted model. Further studies are required to develop better understanding of the mechanisms and pathways through which marriage plays a protective role regarding dementia in different age cohorts. Until then, the results of this study suggest opportunities for social-based interventions that target people living alone that may delay or even reduce the risk of dementia.

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Ethical approval: The Linnaeus database has been approved by the Regional Ethical Committee at Umeå University DNR 07-142Ö.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5, 6
Methods			
Study design	4	Present key elements of study design early in the paper	5, 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, 8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 9, and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7, 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, Table 1 and 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9 and Table 3
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 11, and Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11, 12, 13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.