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Research Article

Loneliness Increases the Risk of All-Cause Dementia and Alzheimer's Disease

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Abstract

Objectives: To examine the effect of perceived loneliness on the development of dementia (all-cause), Alzheimer´s disease (AD), and vascular dementia (VaD).

Method: The study comprised 1,905 nondemented participants at baseline, drawn from the longitudinal Betula study in Sweden, with a follow-up time of up to 20 years (mean 11.1 years). Loneliness was measured with a single question: "Do you often feel lonely?".

Results: During the follow-up, 428 developed dementia; 221 had AD, 157 had VaD, and 50 had dementia of other subtypes. The entire dementia group is denoted "all-cause dementia." Cox regression models, adjusted for age, gender, and a baseline report of perceived loneliness, showed increased risk of all-cause dementia (hazard ratio [HR] = 1.46, 95% confidence interval [CI] 1.14–1.89), and AD (HR = 1.69, 95% CI 1.20–2.37), but not VaD (HR = 1.34, 95% CI 0.87–2.08). After adjusting for a range of potential confounders, and excluding participants with dementia onset within the first 5 years of baseline (to consider the possibility of reverse causality), the increased risk for the development of all-cause dementia and AD still remained significant (HR = 1.51, 95% CI 1.01–2.25 for all-cause dementia; HR = 2.50, 95% CI 1.44–4.36 for AD).

Discussion: The results suggest that perceived loneliness is an important risk factor for all-cause dementia and especially for AD, but not for VaD. These results underscore the importance of paying attention to subjective reports of loneliness among the elderly adults and identifying potential intervention strategies that can reduce loneliness.

Keywords: Living alone, Longitudinal, Risk factors, Social isolation, Social relationship

Life expectancy has increased significantly due to major medical advances (Vaupel, 2010). However, increased longevity has its own set of problems, such as an increase in age-related somatic- and neurocognitive diseases, including dementia, which often incur vast economic and health care-related challenges. The number of people with dementia is expected to increase threefold within the next 30 years, from 50 million to about 152 million by 2050 (Alzheimer´s Disease International, 2018). Currently, there is no effective treatment for dementia, even though lifestyle factors have been shown to play a potentially important role in prevention (Khoury et al., 2019).

Global demographic aging is also accompanied by an increasing number of people living alone, which is a well-known risk factor for social isolation and perceived loneliness (Lam et al., 2017), impacting health and well-being (Cacioppo et al., 2015; Hawkley & Cacioppo, 2010; Holt-Lunstad et al., 2010). A recent meta-analytic review

showed that loneliness increases the risk of all-cause mortality by a magnitude on par with other well-known risk factors, such as obesity and physical inactivity (Holt-Lunstad et al., 2015).

Loneliness should be distinguished from social isolation (Cacioppo et al., 2015). Whereas social isolation is considered an objective condition that arises when someone does not have enough people around, measured through type of living arrangements and marital status, loneliness is referred to as a subjective distressing feeling of alienation. Hence, one can be socially isolated without feeling lonely, or feel lonely without being social isolated. Perceived loneliness in itself is associated with physical health, including increased risk of cardiovascular disease, all-cause mortality, elevated blood pressure, and heightened inflammatory and metabolic responses to stress (Steptoe et al., 2013). Some studies suggest that perceived loneliness has a stronger impact on adverse health outcomes than mere social isolation (Cacioppo et al., 2009), whereas other studies do not (Steptoe et al., 2013).

A number of studies have shown that social isolation is a risk factor for dementia (see e.g., Håkansson et al., 2009; Sundström et al., 2016). Fewer studies have been conducted on perceived loneliness and dementia, however, with conflicting results. A meta-analysis of four longitudinal studies found no association between loneliness and dementia (Penninkilampi et al., 2018), whereas other studies have found that loneliness is associated with increased risk of developing dementia (Rafnsson et al., 2020; Sutin et al., 2018; Zhou et al., 2017). Furthermore, loneliness has cross-sectionally been associated with a higher cortical amyloid burden, a neuropathological feature of AD (Donovan et al., 2016). These inconsistent results probably reflect differences in methodology, such as length of follow-up, adjustment for confounders, and different diagnostic criteria of dementia.

Since dementia exhibits a long preclinical phase, cognitive decline can have a highly variable effect on perceived loneliness as well as social interactions. Therefore, it is essential to conduct studies on risk estimations as many years as possible ahead of the dementing process, as social, behavioral, and a broad range of negative cognitive consequences precludes accurate measures of the amount of social interactions and perceived loneliness (Holwerda et al., 2014; Wilson et al., 2007; Zhoe et al., 2017). Thus, if measures of these factors occur too close to the dementing process, results could be a consequence rather than causative for dementia (i.e., reverse causation).

Previous studies on loneliness have addressed all-cause dementia or AD, but few, if any, have evaluated whether loneliness increases the risk of vascular dementia (VaD). However, loneliness has in a recent meta-analysis been considered to be a risk factor for coronary heart disease and stroke (Valtorta et al., 2016), and heart disease and cardiovascular risk factors are in turn associated with risk of dementia, especially VaD (Justin et al., 2013). Loneliness is also closely associated with depression (Cacioppo et al., 2009), and depression is suggested to increase the risk of developing dementia (for review, see Bennett & Thomas, 2014), possibly even more so for VaD (Barnes et al., 2012). Thus, there are reasons to believe that loneliness can be associated with increased risk of VaD.

The aim of this study was to examine whether perceived loneliness, measured up to 20 years prior to dementia diagnosis, in a longitudinal population-based sample, increases the risk of all-cause dementia, AD, and VaD. To address the issue of reverse causality, sensitivity analyses will be carried out where individuals diagnosed with dementia within the first 1 to 5 years after the study baseline will be excluded. Thereby, the risk that loneliness constitutes a preclinical symptom of dementia will be less likely. Moreover, when examining the effect of loneliness in relation to dementia, it is important to consider presence of depression. Other potential pathomechanisms between loneliness and neurocognition/dementia, e.g., cardiovascular- and lifestyle risk factors, should also be considered in this context.

Method

Study Setting and Participants

The participants were drawn from the Betula Prospective Cohort Study, a longitudinal population-based study in the Umeå municipality in Sweden. For a detailed description of the Betula project's procedure and design, see Nilsson et al. (1997, 2004). In short, the Betula study began in 1988 and includes six samples (Samples S1–S6) and six test waves (Test waves T1–T6), approximately 5 years apart: 1988–1990 (T1 include S1), 1993–1995 (T2, include S1, S2, S3), 1998–2000 (T3, include S1, S2 (part), S3, S4), 2003–2005 (T4, include S1, S3, S5), 2008–2010 (T5, include S1, S3, S6), and 2013–2014 (T6, include S1, S3, S6). All participants in the Betula project were randomly selected from the population registry, stratified by age and gender.

The present study initially included 2,066 participants, aged 60 years, and over at study baseline. All the included participants belonged to samples S1 to S5. The baseline for this study was set to test Wave 3 (for S1–S4), and test Wave 4 (for S5) as a depression scale was introduced in the Betula project at that time, and we wanted to include depression as a covariate in our analyses, since it typically correlates with loneliness (Cacioppo et al., 2009).

Excluded participants were those that had a follow-up time of less than 1 year from the study baseline (n = 44), incomplete information on the questionnaire regarding loneliness (n = 45), or unknown dementia status at follow-up, e.g., due to moving from the catchment area (n = 72). This left a final sample for the present study comprising 1,905 participants.

Measures

Loneliness

The measure of loneliness comprised one single question: "Do you often feel lonely?." Response options for this

question were Yes and No. A single question to measure loneliness is commonly used in this study area and has been shown to correlate highly with multi-item scales (Pinquart & Sörensen, 2001).

Dementia diagnosis assessment

In the Betula project, the diagnostic evaluation of dementia was performed on all study participants at baseline and thereafter every 5 years adjacent to each test waves (T1–T6). A senior research geriatric psychiatrist (coauthor R.A.) coordinated the diagnostic assessments for the entire study period and was responsible for the final diagnoses. The evaluation of dementia served multiple purposes; to identify new dementia cases and determine subtype and year of disease onset, to rule out presence of dementia at study enrolment, and importantly also to confirm a previously determined diagnose and onset. The latter, which is to be regarded as quality assurance of previously performed assessments, was accomplished by that diagnoses and onset was assessed blindly, that is, without knowledge of which diagnosis and age at onset the individual received 5 years earlier. In case a diagnosis did not correspond to the previously given, a second assessment was performed at a separate stage in order to establish a conclusive status.

The diagnoses were ascertained through a process based on diverse sources of information; extensive reading of medical records from multiple clinical disciplines within the county, mainly from the primary care unit, and the medicine-, neurology-, and geriatric clinics. Thus, other clinicians' opinions, information on medical history and current medical status, medication, and the results from available neuroradiological examinations, such as Computed Tomography (CT), Single Photon Emission Computed Tomography (SPECT), and Magnetic Resonance Imaging (MR) were integrated in the assessment.

In addition, for study participants taking part in the health- and cognitive test assessments, neuropsychological testing, structured interviews, and evident clinical signs of neurocognitive impairment observed at each test occasion were collateral information included in the diagnostic decision process. Special attention was given to those who met one or several of the following predefined criteria; low score (≥1.8 standard deviations, SDs, below age-based norms) on a composite cognition and memory test, with a decline in cognitive performance from a previous test occasion (from high to average or low or from average to low); a low score (≤ 23) or a drop by three points, compared with previous score, on the Mini-Mental State Examination (MMSE); self-reported memory failure or staff's suspicion of incipient dementia. Notably, the dementia subtypes AD and VaD were not set unless the clinical picture was characterized by a typical progressive course. Disease onset was defined as the time at which an individual fulfilled the core criteria for dementia, i.e., when the clinical symptoms manifested to the extent that they became sufficiently severe to adversely interfere with social functioning and instrumental activities of daily living (McKhann et al., 2011). Diagnoses were defined in accordance with the criteria for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2000). In total, only 19 participants (0.4%) across all test waves have been improperly included, supporting the validity of the diagnostic evaluation method.

In the present study, all participants with a dementia diagnosis were included, providing other inclusion criteria were met. The dementia subtypes AD (n = 221) and VaD (n = 157) were analyzed as separate/individual groups and also as part of the group identified as all-cause dementia (n = 428), which in addition to AD and VaD also included the dementia subtypes dementia not otherwise specified (n = 21), dementia with Lewy bodies (n = 12), Parkinson´s disease dementia (n = 10), frontotemporal dementia (n = 5), progressive supranuclear palsy (n = 1), and corticobasal degeneration (n =1).

Covariates

Potential covariates, collected at baseline and considered in the previous literature as being related to dementia, were included: age, sex, education (years), marital status (married/nonmarried), smoking (smokers/nonsmokers), alcohol (yes, never drank, or no had quit), and previous cardiovascular disorders (the total number of self-reported heart disease, stroke, hypertension, and diabetes during the last 5 years).

We used the 20-item Center for Epidemiologic Studies Depression Scale, CES-D (Radloff, 1977) to assess the symptoms of depression. The CES-D scale is a self-report scale that consists of 20 statements' addressing depressive symptoms. The participants indicate how often, during the last 7 days, they experienced those symptoms on a 4-grade scale, ranging from 0 (rarely or none of the time) to 3 (most or all of the time). One item in the CES-D scale asks whether the participants felt lonely so this item was excluded before calculating a total score. The CES-D scale is considered to have good psychometric properties in an older population, and a cutoff score of 16 is commonly used to identify individuals with a clinically relevant level of depressive symptoms (Berkman et al., 1986). This cutoff score has been found to have high sensitivity (100%) and high specificity (88%; Beekman et al., 1997) for identifying depressive individuals.

Statistical Analyses

Background characteristics of participants who developed dementia during follow-up and those who remained nondemented were analyzed using Chi-square tests for the categorical variables and a Student's t-test for the continuous variables. To study the association between loneliness and the risks of all-cause dementia, AD, and VaD, separate multivariate-adjusted Cox proportional hazard models were used. In Model 1, adjustments were made

for age and gender; in Model 2, additional adjustments were made for education, marital status, smoking, alcohol use, self-reported cardiovascular disorders, and depressive symptoms. Finally, to consider the possibility of reverse causation bias, a sensitivity analysis was done in Model 3 by excluding all participants with a survival time of 5 years or less from the study baseline. Hence, in Model 3, adjustments were made for all covariates in Model 2, after excluding participants with a survival time that fell within the first five years from the study baseline.

The proportional hazard assumptions were evaluated using graphic methods and were met for all models. Time to event was calculated as date of first entry into the present study (i.e., test wave T3 for S1–S4 and test wave T4 for S5) to the date of final follow-up (2016) or the time when the participants either received a dementia diagnose, died, or were lost to follow-up, depending on which event came first. These results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and considered as significant at $p < .05$. All statistical analyses were two-sided and performed using the Statistical Package for Social Science (SPSS) Version 24.0.

Results

The baseline characteristics for the study population are presented in Table 1. Participants were followed-up for a mean of 11.1 years (*SD* 5.6, median 12.0, range 1–20). During follow-up, 428 participants developed dementia; 221 with AD, 157 with VaD, and 50 of other subtypes as specified in the methods section. Compared to participants who did not develop dementia, those who did were older, more often females, had fewer years of schooling (significant only for all-causes and AD), and were more likely to be married. Moreover, they drank less alcohol (significant only for all-causes and VaD), had more previous cardiovascular disorders (significant only for VaD), had fewer previous cardiovascular disorders (significant only for AD), reported more depressive symptoms (significant only for all-causes and AD), and reported more often that they felt lonely (significant only for all-causes and AD), see Table 1.

The impact of perceived loneliness on the incidence of all-cause dementia, AD, and VaD,was evaluated using separate Cox proportional regression models, adjusted for a range of covariates, see Table 2. In Model 1, adjusted for age and sex, perceived loneliness was significantly related to an increased risk of all-cause dementia (HR = 1.46, 95% CI 1.14–1.89) and AD (HR = 1.69, 95% CI 1.20–2.37), but not to VaD (HR = 1.34, 95% CI 0.87–2.08). Additional adjustment in Model 2 for education, marital status, smoking, alcohol use, previous cardiovascular diseases/disorders, and depressive symptoms yielded similar results with significant results for all-causes dementia (HR = 1.38, 95% CI 1.04–1.84) and AD (HR=1.83, 95% CI 1.25–2.67 for AD).

Model 3 included all adjustments as in Model 2, but in addition, a sensitivity analysis was performed by excluding participants with dementia onset within the first 5 years from baseline. Model 3 included a sample of 1,428

Table 1. Study Participant Baseline Characteristics

Characteristic	No dementia, *n* = 1,477	Incident dementia during follow-up		
		All-cause *n* = 428	AD *n* = 221	VaD *n* = 157
Age, mean ± *SD*	71.5 (9.3)	74.7 (7.6)***	74.5 (7.6)***	75.2 (6.9)***
Female, *n* (%)	777 (52.6)	278 (65.0)***	155 (70.1)***	97 (61.8)*
Education (years), mean ± *SD*	8.9 (3.6)	8.4 (3.4)*	8.2 (3.1)**	8.6 (3.8)
Married, *n* (%)	947 (64.2)	230 (53.9)***	120 (54.3)***	82 (52.6)**
Current smoking, *n* (%)				
No	802 (54.3)	243 (56.8)	131 (59.3)	86 (54.8)
Yes	674 (45.7)	185 (43.2)	90 (40.7)	71 (45.2)
Alcohol use, *n* (%)				
No, never drank or have quit	359 (24.4)	128 (29.9)*	67 (30.3)	51 (32.5)*
Yes	1,115 (75.6)	300 (70.1)*	154 (69.7)	106 (67.5)*
Number of previous cardiovascular disorders, mean ± *SD*	0.8 (0.9)	0.8 (0.8)	0.7 (0.8)*	1.0 (0.9)*
Depressive symptoms, *n* (%)				
CES-D, score 15 or less	1,327 (89.8)	37 (88.6)*	184 (88.9)**	140 (89.2)
CES-D, score 16 or more	110 (6.8)	44 (10.3)*	21 (10.1)**	15 (9.6)
Perceived loneliness, *n* (%)				
No	1,319 (89.3)	352 (82.2)***	177 (80.1)***	132 (84.1)
Yes	158 (10.7)	76 (17.8)***	44 (19.9)***	25 (15.9)

Notes: Missing values: Education (21), marital status (4), alcohol use (3), and depressive symptoms (54). Test of difference between the group without dementia at follow-up and all-cause dementia, AD, or VaD, were conducted using t-tests (continuous variables) or χ^2-tests (categorical variables).
* $p < .05$; ** $p < .01$, *** $p < .001$.

Table 2. Cox Proportional Hazard Regressions Models of Incident All-Cause Dementia, Vascular Dementia, and Alzheimer's Disease by Perceived Loneliness With Additional Adjustment for Potential Covariates

	Total no. of participants	No. of cases	Hazard ratio (95% Confidence Interval)	*p* value
All-cause dementia				
Model 1[a]	1,905	428	1.46 (1.14–1.89)	.003
Model 2[b]	1,826	420	1.38 (1.04–1.84)	.024
Model 3[c]	1,428	247	1.53 (1.02–2.27)	.038
Alzheimer's disease				
Model 1[a]	1,698	221	1.69 (1.20–2.37)	.003
Model 2[b]	1,624	218	1.83 (1.25–2.67)	.002
Model 3[c]	1,298	117	2.53 (1.45–4.40)	.001
Vascular dementia				
Model 1[a]	1,636	157	1.34 (0.87–2.08)	.189
Model 2[b]	1,558	152	1.08 (0.66–1.77)	.758
Model 3[c]	1,282	101	1.01 (0.51–1.99)	.973

Notes: [a]Model 1 was adjusted for age and sex.
[b]Model 2 was adjusted for age, sex, education, marital status, smoking, alcohol use, previous cardiovascular disorders, and depressive symptoms.
[c]Model 3 was adjusted for the same covariates as in model 2 after excluding all cases within the first 5 years since follow-up.

participants, with a mean follow-up time of 13.5 years (SD 3.8, median 14.0, range 6–20). Excluding participants with near onset of dementia did not diminish the association between loneliness and all-cause dementia (HR = 1.53, 95%, CI 1.02–2.27) and AD (HR = 2.53, 95%, CI 1.45–4.40).

Discussion

This prospective population-based study examined the association between perceived loneliness and incident dementia with up to 20 years of follow-up. The results show that participants who reported feeling often lonely had an increased risk of developing all-cause dementia and AD. Adjustment for sociodemographic and health factors, including baseline depressive symptoms, did not alter the association. The observed results persist also following removal of participants who developed dementia within the first 5 years after study baseline, and whose loneliness may have been a symptom of preclinical dementia, were excluded. Notably, no association was observed between loneliness and VaD.

The results of this study are in line with most previous studies also reporting loneliness as a risk factor for the development of all-cause dementia (Holwerda et al., 2014; Rafnsson et al., 2020; Sutin et al., 2018; Wilson et al., 2007; Zhou et al., 2018). In this study, we further demonstrated that perceived loneliness is a risk factor particularly for AD, but not for VaD. As far as we know, this is the first study that considers risk estimates between the two most common subtypes of dementia. Although prior studies have not specifically studied the association with various subtypes of dementia, one previous study found loneliness to be associated with increased risk of AD (Wilson et al., 2007). In addition, a study of cognitively healthy elderly adults found greater loneliness to be significantly associated with higher cortical amyloid burden (Donovan et al., 2016), which is considered to be one of the main components of plaque involved in AD (Palop & Mucke, 2010), and thus implies a connection between AD pathophysiology and loneliness (Donovan et al., 2016). But further large-scale studies are needed to evaluate the association between loneliness and dementia subtypes before any firm conclusion can be drawn.

Our findings that the relationship between loneliness and dementia persisted after controlling for depressive symptoms are in agreement with other studies (Holwerda et al., 2014; Rafnsson et al., 2020; Sutin et al., 2018; Wilson et al., 2007) and also corroborate with studies suggesting loneliness to be a concept distinct from depression (VanderWeele et al., 2011). The results suggest that the effects of loneliness on dementia may not go through depression, as some previous studies using cognitive status as end-point have argued (Gow et al., 2013; Lam et al., 2017).

The long follow-up time of this study makes it possible to consider the eventual impact of reverse causality, i.e., that loneliness is a symptom of dementia instead of a risk factor for dementia. In this study, excluding participant with near onset of dementia, did not remove the association between loneliness and dementia, thereby suggesting that the association is less likely to be explained by reverse causality, although it cannot be completely ruled out, since dementia develops over a long time period (Barnett et al., 2013; Jansen et al., 2015). Furthermore, two recently published longitudinal studies examining the effect of loneliness on dementia have also been able to address the issue of reverse causality, and excluding participants who received a dementia diagnosis within the first 4 (Rafnsson et al., 2020) and 6 years (Sutin et al., 2018) after baseline. Interestingly, the results of these two studies were shown, as in our study, to persist also after excluding people close to dementia onset, and thereby add additional support to the hypothesis that loneliness can increase the risk of developing dementia and is not just a prodromal feature of dementia.

A common hypothesis in the literature on the association between social relationships (including social isolation and perceived loneliness) and dementia takes its starting point from the "use it or lose it" theory, suggesting that engagement in, for example social and cognitive activities, has a stimulating effect on the brain, and that less activity may result in brain atrophy (Hultsch et al., 1999). Closely related to the theory of "use it or lose it" is the cognitive reserve theory (Scarmeas & Stern, 2004). According to the model of cognitive reserve, environmental factors such as social interaction may stimulate the neurogenesis and synaptic density of the brain and could leave an individual with a larger cognitive reserve, resulting in a more efficient

cognitive network. This in turn would enable more efficient utilization of brain networks and/or enhanced ability to recruit alternative networks to compensate for age-related neural changes or neurological pathology (Stern, 2002).

A more recent model of loneliness and its effect on health posits that loneliness is equivalent to feeling unsafe, which unconsciously makes individuals more sensitive to potential social threats in the environment and to experience the social world as more threatening (Hawkley and Cacioppo, 2010). Research has shown that a lonely individual's chronic perception of social threat may stimulate the sympathetic nervous system, which may affect the immune system by an upregulation of inflammatory genes expression and downregulation of antiviral responses (Cole et al., 2015). Thus, the inflammatory response suggested to be associated with social isolation and loneliness could be a possible pathway linking it to dementia (Gorelick, 2010).

One advantage of this study was its population-based prospective design, with a rather large sample and a long follow-up duration. Other strengths include that dementia diagnoses have been assessed and validated by an experienced clinician in geropsychiatry and were done according to establish criteria. However, even though care has been taken in defining major subtypes of dementia, we were not able to validate the diagnoses by neuropathological examination, but neurological and neuroradiological examinations were included when available in medical records or if part of the Betula MRI/fMRI protocol (n = 376). To minimize the risk of misclassification, diagnoses were evaluated at repeated occasions and reassessed blindly in order to establish a reliable dementia status. Moreover, limitations include also risk of underdiagnoses. However, underdiagnosing may be less of a problem in this study since data obtained from the project have been compared with both inpatient register data and death certificates. Another limitation is the use of a single-item question of loneliness, which may result in underreporting due to the stigma associated with being regarded as lonely (Ong et al., 2016). Nonetheless, in previous research, measuring loneliness with a single question is widely used and has been considered valid (Victor et al., 2005).

In conclusion, loneliness has become increasingly recognized as a major public health problem and increases the risk of premature all-cause mortality. The results of this study suggest that perceived loneliness is a risk factor also for all-cause dementia and especially for AD. Our results underscore the importance of paying attention to perceived loneliness among the elderly adults and to identifying potential interventions that may reduce perception of loneliness.

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Conflict of Interest

None reported.

Data Availability Statement

Data from the Betula project cannot be made publicly available due to ethical and legal restrictions. However, access to these original data is available upon approval by the Steering Group of the Betula study. For further information about accessibility of data, see http://www.org.umu.se/betula/betula/access-betula-data/?languageId=1.

Preregistered

This study was not preregistered.

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