RESEARCH PAPER

Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL)

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ABSTRACT

Background Known risk factors for Alzheimer's disease and other dementias include medical conditions, genetic vulnerability, depression, demographic factors and mild cognitive impairment. The role of feelings of loneliness and social isolation in dementia is less well understood, and prospective studies including these risk factors are scarce.

Methods We tested the association between social isolation (living alone, unmarried, without social support), feelings of loneliness and incident dementia in a cohort study among 2173 non-demented community-living older persons. Participants were followed for 3 years when a diagnosis of dementia was assessed (Geriatric Mental State (GMS) Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT)). Logistic regression analysis was used to examine the association between social isolation and feelings of loneliness and the risk of dementia, controlling for sociodemographic factors, medical conditions, depression, cognitive functioning and functional status.

Results After adjustment for other risk factors, older persons with feelings of loneliness were more likely to develop dementia (OR 1.64, 95% CI 1.05 to 2.56) than people without such feelings. Social isolation was not associated with a higher dementia risk in multivariate analysis.

Conclusions Feeling lonely rather than being alone is associated with an increased risk of clinical dementia in later life and can be considered a major risk factor that, independently of vascular disease, depression and other confounding factors, deserves clinical attention. Feelings of loneliness may signal a prodromal stage of dementia. A better understanding of the background of feeling lonely may help us to identify vulnerable persons and develop interventions to improve outcome in older persons at risk of dementia.

INTRODUCTION

Dementia is a multicausal medical condition with a high and increasing prevalence in both developed and developing countries. Alzheimer's disease and vascular dementia account for ~90% of cases. Known risk factors for dementia include higher age, low education, genetic vulnerability, earlier head injury, mild cognitive impairment, stroke, hypertension, dyslipidaemia, hyperinsulinaemia, type 2 diabetes, obesity, subclinical atherosclerosis, cardiac arrhythmias and Instrumental Activities of Daily Living (IADL) disability.[1 2] Converging evidence suggests that, besides medical conditions, late-onset depression can be both a prodrome and a comorbid condition of cognitive decline and dementia. Among other potential mechanisms, depression may predispose to dementing disorders through hypothalamic–pituitary (HPA) axis hyperactivity and subsequent hippocampal atrophy.[1 3–5] Interestingly, environmental factors such as social isolation—defined as being not or no longer married, living alone, having a small social network, little participation in activities with others, or lack of social engagement (social connections)—have been shown to be associated with cognitive decline and Alzheimer's disease. In contrast, having an extensive social network and social resources were found to be associated with less cognitive decline in old age.[6–10] Fewer studies have focused on emotional predictors such as sensitivity to psychological distress, emotional isolation, dissatisfaction with social interactions, and feelings of loneliness in relation to the onset of dementia. Feelings of loneliness as a potential risk factor for the development of dementia have rarely been investigated. Only two studies showed an association between sensitivity to psychological distress and loneliness and an increased risk of late life dementia.[11 12]

Theoretically, loneliness may be a behavioural reaction to diminished cognition, and thus a direct consequence of more subtle pathology contributing to dementia. Both impaired social cognition and diminished sociocognitive skills are seen in prodromal dementia.[12–14] Loneliness may also lead to a lack of sensory and cognitive stimulation and thereby compromise neural systems underlying cognition, resulting in a decrease in neural reserve.[12] The association between social isolation, feelings of loneliness and subsequent cognitive decline currently raises questions. It is unclear to what extent social isolation (the quantity of social interactions) and feelings of loneliness (a lack of quality of social attachments and the evaluation of being alone as negative) specifically contribute to the onset of dementia, especially when other known risk factors are adjusted for. In the context of rapidly ageing populations and, for many countries, the societal trend towards increasing numbers of single households with risk of social isolation and feeling lonely, further exploration of this factor is relevant from both a theoretical and public health perspective.

The Amsterdam Study of the Elderly (AMSTEL) is a prospective community-based cohort study

examining risk factors for depression, dementia and excess mortality in older persons. The present study examines the association between social isolation, feelings of loneliness and dementia at 3-year follow-up. We adjusted for potentially confounding or explanatory variables that might account for this association, such as demographic factors, medical disorders, depression and functional disabilities. Incident diagnosis of dementia during a 3-year period served as the outcome.

METHODS

Study population

The AMSTEL is a large population-based cohort study in the Netherlands that investigates the incidence, prevalence and determinants of common mental disorders and their prognosis among older persons.[15] The study was approved by the Medical Ethics Committee of VU University Amsterdam. A total of 5666 older persons were randomly selected from 30 general practice registers in the city of Amsterdam. Out of this sample, 4051 (71.5%) participated at baseline (June 1990—November 1991) and, of these, 2244 (55.4%) participated at the 3-year follow-up (median 38 months). Non-response at baseline was associated with poor cognitive functioning in persons 65–75 years old. In persons over the age of 75, no associations with non-response were found.[16 17] At the 3-year follow-up, 656 persons (16.2%) had died, 282 (7.0%) were too ill or cognitively impaired to participate, 662 (16.3%) refused to participate, and 207 (5.1%) were no longer available for other reasons.[16 17] For the present study, participants with dementia at baseline (71, 3.2%) were excluded, leaving 2173 participants for further study.

Measurements

At baseline and follow-up, all participants underwent a home assessment by specially trained and regularly supervised interviewers, using standardised questionnaires on demographic characteristics, medical and psychiatric conditions, cognitive and daily functioning, and other conditions. The interview included questions on sociodemographic items, the Geriatric Mental State Examination, a structured psychiatric interview and diagnostic algorithm (Geriatric Mental State (GMS) Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT)), generating diagnoses of psychiatric disorders with severity ratings of these disorders on five levels. Levels 3–5 represent clinical cases, and levels 1–2 represent subcases. The Cambridge Mental Disorders of the Elderly Examination (CAMDEX) was used to assess present and past medical conditions, psychiatric disorders and cognitive functioning. The interview also contained the Mini Mental State Examination (MMSE), the Activities of Daily Living (ADL) scale, the IADL scale, and questions related to smoking and drinking behaviour.[18–24]

At baseline, social isolation was operationally defined as either living alone or not being/no longer being married or not having social support (question: Do you get help from family, neighbours or home support?). Feelings of loneliness were assessed by the question: Do you feel lonely or do you feel very lonely?

A diagnosis of clinical dementia was defined as having GMS AGECAT scores of level 3 or higher. The GMS AGECAT has shown high levels of sensitivity and specificity and achieved an overall kappa value of 0.88 for organic illness (various stages of dementia) in the community.[18 25 26] Cognitive impairment no dementia (CIND) was defined as GMS AGECAT organic levels 1–2.

Educational level was dichotomised as primary school or less and more than primary school. Depression was defined as GMS AGECAT depression levels 3–5. Generalised anxiety disorder was defined as GMS AGECAT anxiety levels 3–5. Medical conditions were assessed by the relevant CAMDEX questions. Alcohol misuse was defined as four or more units daily during minimally 1 year in the past or present, and smoking was defined as 20 cigarettes/day during minimally 1 year in the past or present. ADL and IADL disability were defined as two or more points below the maximum score on the respective scales.

Data analysis

First, the prevalence of all baseline conditions possibly associated with dementia was assessed. We computed collinearity statistics as part of the procedure.[27] Second, in bivariate analysis, ORs were calculated for the association between incident dementia and all potential risk factors, including social isolation and feelings of loneliness. We also analysed the association between feelings of loneliness and dementia in socially isolated subgroups and in men and women. We calculated mean MMSE scores at baseline and at follow-up both in the whole sample and separately in the participants feeling lonely and not feeling lonely. Third, in multivariate analysis, the association between social isolation factors and feelings of loneliness, and onset of dementia was assessed using multiple logistic regression analysis, with stepwise adjustment for demographic factors (age, gender, level of education), other social isolation factors and/or feelings of loneliness, depression (also including subthreshold depression), cardiovascular conditions, other medical disorders, cognitive functioning and functional disabilities (ADL and IADL). ORs for incident all-cause dementia were calculated. In order to control for possible confounding by depressive symptoms, bivariate associations and interactions between feelings of loneliness and depression and between individual social isolation factors and depression were assessed using both a dichotomous and continuous depression variable incorporating the five severity/caseness levels provided in GMS AGECAT. Also, an interaction between feelings of loneliness and IADL dependency was analysed. If such an interaction effect was found, an interaction term was added to the model in multivariate analysis. Finally, a parsimonious model was created for the development of dementia using backstep logistic regression analysis; the criterion for excluding variables was set at $p<0.05$.

RESULTS

Characteristics of cohort

At baseline, 1005 (46.2%) participants were living alone, 1100 (50.6%) were not or no longer married, and 1590 (73.2%) were not receiving social support. A total of 433 (19.9%) older persons reported feelings of loneliness. Baseline sample characteristics are shown in table 1.

Social isolation, feelings of loneliness and incident dementia

Of the participants living alone at baseline, 9.3% had developed dementia at 3 years follow-up compared with 5.6% of participants living with others ($p=0.001$). Of participants not or no longer married, 9.2% had developed dementia compared with 5.3% of those who were married ($p=0.001$). Of participants without social support, 5.6% had developed dementia compared with 11.4% of those receiving social support ($p=0.000$). Of participants with feelings of loneliness at baseline, 13.4% met criteria for dementia at 3 years compared with 5.7% of participants without such feelings ($p=0.000$). Bivariate analysis

Table 1 Baseline sample characteristics of 2173 participants

Variable	n (%)
Social isolation	
Living alone	1005 (46.2)
Not/no longer married	1100 (50.6)
Lack of social support	1590 (73.2)
Feelings of loneliness	433 (19.9)
Sex	
Men	801 (36.9)
Women	1372 (63.1)
Age	
65–69	533 (24.5)
70–74	574 (26.4)
75–79	568 (26.1)
80–86	498 (22.9)
Education	
>Primary school	1370 (63.0)
Primary school or less	803 (37.0)
CIND	75 (3.5)
Depression	233 (10.7)
Generalised anxiety disorder	59 (2.7)
Ischaemic heart disease	195 (9.0)
Cerebrovascular disease	101 (4.6)
Diabetes	163 (7.5)
Hypertension	533 (24.5)
Cardiac arrhythmia	420 (19.3)
Respiratory disease	321 (14.8)
Cancer	233 (10.7)
Epilepsy	29 (1.3)
Parkinson's disease	21 (1.0)
Arthritis/arthrosis	388 (17.3)
Alcohol misuse	104 (4.8)
Smoking	563 (25.9)
Traumatic brain injury	190 (8.7)
MMSE	
26–30	1956 (90.0)
22–25	194 (8.9)
0–21	23 (1.1)
ADL disability	103 (4.7)
IADL disability	393 (18.1)

ADL, activities of daily living; CIND, cognitive impairment no dementia; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination.

(table 2) showed participants living alone (OR 1.72, 95% CI 1.24 to 2.40) and those not or no longer married (OR 1.80, 95% CI 1.29 to 2.52) to have an increased risk of dementia compared with participants living with others and those who were married, respectively. Not having social support showed a lower risk of dementia (OR 0.46, 95% CI 0.33 to 0.64) in bivariate analysis. Feelings of loneliness were associated with an increased risk of dementia (OR 2.56, 95% CI 1.82 to 3.61). No interactions were found between feelings of loneliness, living alone, not/no longer being married, no social support and sex at baseline (p=0.50, 0.84, 0.80, 0.61, respectively), indicating no differences between men and women in developing dementia. Age, educational level, CIND, depression, cerebrovascular disease, respiratory disease and functional impairment were also associated with an increased risk of dementia in bivariate analysis.

Subgroup analysis showed that, in both socially isolated (living alone, not/no longer married, not receiving social support) and not socially isolated (married and receiving social support) subgroups, the bivariate association between feelings of loneliness and incident dementia was statistically significant. Only in the subgroup of participants living with others were feelings of loneliness not associated with dementia (table 3).

We found that the mean MMSE score of all participants was 27.94 (SD 1.94) at baseline and 26.81 (SD 3.09) at follow-up; the decrease in MMSE was more pronounced in those with feelings of loneliness (MMSE score at baseline 27.52 (SD 2.12); at follow-up 25.84 (SD 4.11)) than those without feelings of loneliness (MMSE score at baseline 28.05 (SD 1.84); at follow-up 27.06 (SD 2.71)).

In bivariate analysis, no interactions were found between living alone, not/no longer being married and not receiving social support and the dichotomous and continuous depression variable at baseline (p=0.79, 0.51, 0.52, 0.95, 0.22, 0.47, respectively), and no interactions were found between feelings of loneliness and the dichotomous and continuous depression variable at baseline (p=0.51 and p 0.51, respectively). Also no interaction was found between feelings of loneliness and IADL independence (p=0.84).

In multivariate analysis, the association between the social isolation factors, feelings of loneliness and incident dementia was examined with stepwise adjustment for potential confounding and explanatory variables. The adjusted OR in the final model was 1.64 (95% CI 1.05 to 2.56) for feelings of loneliness, signifying an increased risk of incident dementia (table 4). No associations were found with dementia in socially isolated persons living alone, not or no longer married and not having support in multivariate analysis (table 4).

In a backstep logistic regression analysis, all factors associated with dementia in bivariate analysis were entered. This yielded a parsimonious model consisting of the variables, age, MMSE score, CIND, IADL disability and feelings of loneliness (Nagelkerke R^2=0.194, table 5). The explained variance of this model was 19%. Using a p out value of 0.10 did not alter these findings. Repeating the backstep logistic regression analysis without the variable feelings of loneliness resulted in a best fitting model consisting of age, MMSE score, CIND and IADL disability.

DISCUSSION

In our cohort of 2173 non-demented older persons with a 3-year follow-up of dementia, a higher risk was found for two determinants of social isolation (living situation and marital status), as well as for the subjective experience of feeling lonely. In multivariate analysis, controlling for a comprehensive set of demographic, somatic and psychiatric risk factors, individuals with feelings of loneliness remained 1.64 times more likely to develop clinical dementia than persons who did not feel lonely. In contrast, objective aspects of social isolation no longer showed such an association.

These results suggest that feelings of loneliness independently contribute to the risk of dementia in later life, an effect that may be due to mechanisms other than those in vascular or Alzheimer pathology or a depression-related (HPA axis hyperactivity) mechanism. Indeed, our data show that a model consisting of age, two aspects of baseline cognitive functioning (MMSE and CIND), functional disabilities and feelings of loneliness predicted 19% of the variance in incident dementia at follow-up.

Interestingly, the fact that 'feeling lonely' rather than 'being alone' was associated with dementia onset suggests that it is not the objective situation, but rather the perceived absence of social attachments that increases the risk of cognitive decline. Previous

Table 2 Bivariate associations of risk factors with clinical dementia (OR with 95% CI) (N=158)

Variable	Dementia (n (%))	Dementia (OR (95% CI))
Social isolation		
Living alone		**1.72 (1.24 to 2.40)**
Yes (n=1005)	93 (9.3%)	
No (n=1166)	65 (5.6%)	
Not/no longer married		**1.80 (1.29 to 2.52)**
Not/no (n=1100)	101 (9.2)	
Married (n=1071)	57 (5.3)	
Social support		**0.46 (0.33 to 0.64)**
No (1590)	89 (5.6)	
Yes (578)	66 (11.4)	
Feelings of loneliness		**2.56 (1.82 to 3.61)**
Yes (n=433)	58 (13.4)	
No (n=1737)	99 (5.7)	
Age		
65–69 (533)*	8 (1.5)	
70–74 (574)	23 (4.0)	**2.74 (1.21 to 6.18)**
75–79 (568)	56 (9.9)	**7.18 (3.39 to 15.21)**
80–86 (498)	71 (14.3)	**10.92 (5.20 to 22..92)**
Sex		1.14 (0.81 to 1.60)
Women (1372)	104 (7.6)	
Men (801)	54 (6.7)	
Educational level		**1.94 (1.40 to 2.68)**
Primary school or<(803)	82 (10.2)	
>Primary school (1370)	76 (5.5)	
CIND		**5.99 (3.54 to 10.14)**
Yes (75)	22 (29.3)	
No (2098)	136 (6.5)	
Depression		**1.99 (1.30 to 3.06)**
Yes (233)	29 (12.4)	
No (1940)	129 (6.6)	
Generalised anxiety disorder		0.93 (0.33 to 2.59)
Yes (59)	4 (6.8)	
No (2114)	154 (7.3)	
Ischaemic heart disease		1.16 (0.67 to 1.98)
Yes (195)	16 (8.2)	
No (1978)	142 (7.2)	
Cerebrovascular disease		**2.35 (1.33 to 4.18)**
Yes (101)	15 (14.9)	
No (2072)	143 (6.9)	
Diabetes		1.02 (0.55 to 1.87)
Yes (163)	12 (7.4)	
No (2010)	146 (7.3)	
Hypertension		0.64 (0.42 to 0.98)
Yes (533)	28 (5.3)	
No (1640)	130 (7.9)	
Cardiac arrhythmia		0.85 (0.55 to 1.31)
Yes (420)	27 (6.4)	
No (1751)	131 (7.5)	
Epilepsy		1.48 (0.44 to 4.95)
Yes (29)	3 (10.3)	
No (2144)	155 (7.2)	
Parkinson's disease		2.15 (0.63 to 7.37)
Yes (21)	3 (14.3)	
No (2152)	155 (7.2)	
Respiratory disease		**1.52 (1.01 to 2.28)**
Yes (321)	32 (10.0)	
No (1852)	126 (6.8)	
Cancer		0.87 (0.50 to 1.50)
Yes (233)	15 (6.4)	
No (1940)	143 (7.4)	
Arthrosis/arthritis		1.24 (0.83 to 1.86)
Yes (375)	32 (8.5)	
No (1798)	126 (7.0)	
Alcohol misuse		0.85 (0.39 to 1.87)
Yes (104)	7 (6.7)	
No (1545)	121 (7.8)	
Smoking		0.74 (0.50 to 1.10)
Yes (563)	33 (5.9)	
No (1609)	125 (7.8)	
Traumatic brain injury		0.69 (0.36 to 1.33)
Yes (190)	10 (5.3)	
No (1982)	148 (7.5)	
MMSE		
26–30 (1956)*	101 (5.2)	
22–25 (194)	47 (24.2)	**5.87 (4.00 to 8.63)**
0–21 (23)	10 (43.5)	**14.13 (6.05 to 33.00)**
ADL disability		**2.92 (1.71 to 4.99)**
Yes (103)	18 (17.5)	
No (2070)	140 (6.8)	
IADL disability		**3.39 (2.41 to 4.76)**
Yes (393)	63 (16.0)	
No (1780)	95 (5.3)	

Clinical dementia after 3 years of follow-up: % clinical dementia and OR with 95% CI. Significant OR in bold.
*Reference category.
ADL, activities of daily living; CIND, cognitive impairment no dementia; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination.

research on this issue has mainly focused on social isolation, the physical absence of other persons defined by factors such as social network, social resources and activities.[6 8–10 28–30] Much less work has been carried out on the subjective experience defined as dissatisfaction with social relationships, social needs and perceived loneliness as predictors of dementia. To our knowledge, only one study assessed an association between feelings of loneliness and cognitive decline,[31] and one study assessed an increased risk of late-life dementia in participants with loneliness according to the De Jong Gierveld Loneliness Scale.[12] Unlike the present study, these studies did not adjust for an extensive number of potential risk factors,[31] had lower numbers of lonely participants, and did not make a distinction between social isolation and feelings of loneliness.[12 31]

Table 3 Bivariate associations of feelings of loneliness in socially isolated subgroups

Feelings of loneliness in participants	Dementia (OR (95% CI))
Living alone	**2.52 (1.63 to 3.89)**
Living with others	1.67 (0.74 to 3.80)
Not/no longer married	**2.24 (1.48 to 3.39)**
Married	**2.31 (1.05 to 5.07)**
Not receiving social support	**2.03 (1.24 to 3.31)**
Receiving social support	**2.47 (1.47 to 4.16)**

Clinical dementia after 3 years of follow-up. Significant OR in bold.

Table 4 Association between feelings of loneliness and incident dementia with stepwise adjustment for other potential risk factors

	OR (95% CI)		OR (95% CI)
Feelings of loneliness (unadjusted ratio)	**2.48 (1.76 to 3.51)**	Living alone (unadjusted ratio)	**1.75 (1.25 to 2.44)**
Stepwise adjustment for:			
Living alone	**2.19 (1.50 to 3.19)**	Feelings of loneliness	1.35 (0.94 to 1.94)
Not/no longer married	**2.17 (1.49 to 3.16)**	Not/no longer married	0.94 (0.49 to 1.82)
No social support	**2.05 (1.40 to 3.00)**	No social support	0.92 (0.48 to 1.76)
Age	**1.97 (1.34 to 2.90)**	Age	0.90 (0.46 to 1.73)
Sex and educational level	**1.96 (1.33 to 2.89)**	Sex, age and educational level	0.90 (0.47 to 1.75)
Depression (including subthreshold depression)	**1.69 (1.11 to 2.60)**	Depression (including subthreshold depression)	0.94 (0.49 to 1.81)
Ischaemic heart disease, cerebrovascular disease, diabetes, hypertension and cardiac arrhythmias	**1.66 (1.08 to 2.53)**	Ischaemic heart disease, cerebrovascular disease, diabetes, hypertension and cardiac arrhythmias	0.98 (0.51 to 1.90)
COPD and Parkinson's disease	**1.64 (1.08 to 2.51)**	COPD and Parkinson's disease	0.96 (0.50 to 1.86)
Traumatic brain injury	**1.63 (1.07 to 2.50)**	Traumatic brain injury	0.95 (0.49 to 1.84)
Cognitive impairment no dementia	**1.67 (1.09 to 2.57)**	Cognitive impairment no dementia	0.98 (0.50 to 1.92)
MMSE	**1.68 (1.08 to 2.61)**	MMSE	0.93 (0.46 to 1.86)
Functional impairment (ADL and IADL)	**1.64 (1.05 to 2.56)**	Functional impairment (ADL and IADL)	0.96 (0.48 to 1.93)
Not/no longer married (unadjusted ratio)	**1.83 (1.30 to 2.58)**	No social support (unadjusted ratio)	**0.45 (0.32 to 0.63)**
Stepwise adjustment for:			
Feeling of loneliness	**1.45 (1.01 to 2.09)**	Feelings of loneliness	**0.51 (0.36 to 0.72)**
Living alone	1.53 (0.79 to 2.95)	Living alone	**0.53 (0.37 to 0.75)**
No social support	1.38 (0.72 to 2.65)	Not/no longer married	**0.54 (0.38 to 0.76)**
Age	1.09 (0.56 to 2.12)	Age	0.71 (0.50 to 1.02)
Sex, age and educational level	1.18 (0.60 to 2.31)	Sex, age and educational level	0.71 (0.50 to 1.03)
Depression (including subthreshold depression)	1.15 (0.59 to 2.24)	Depression (including subthreshold depression)	0.74 (0.52 to 1.07)
Ischaemic heart disease, cerebrovascular disease, diabetes, hypertension and cardiac arrhythmias	1.09 (0.56 to 2.13)	Ischaemic heart disease, cerebrovascular disease, diabetes, hypertension and cardiac arrhythmias	0.74 (0.51 to 1.07)
COPD and Parkinson's disease	1.11 (0.57 to 2.18)	COPD and Parkinson's disease	0.75 (0.52 to 1.08)
Traumatic brain injury	1.12 (0.57 to 2.19)	Traumatic brain injury	0.74 (0.51 to 1.08)
CIND	1.16 (0.59 to 2.31)	Cognitive impairment no dementia	0.78 (0.53 to 1.13)
MMSE	1.24 (0.61 to 2.51)	MMSE	0.89 (0.61 to 1.32)
Functional impairment (ADL and IADL)	1.23 (0.61 to 2.50)	Functional impairment (ADL and IADL)	1.06 (0.70 to 1.60)

Logistic regression, 95% CI, results for feelings of loneliness versus no feelings of loneliness. Significant OR in bold.
ADL, activities of daily living; CIND, cognitive impairment no dementia; COPD, chronic obstructive pulmonary disease; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination.

The explanation for an association between feelings of loneliness and incident dementia is tentative. It has been hypothesised that loneliness may affect cognitive and memory systems by reducing cognitive activity and decreasing neural reserve through decreased dendritic arborisation in hippocampal and prefrontal areas, resulting in downregulation of brain-derived neurotrophic factor accompanied by impaired memory and concept formation.[12] Another possibility is that loneliness may be a consequence of preclinical dementia, either as a behavioural reaction to impaired cognition or as a consequence of undetected pathology contributing to dementia.[12] Interacting socially (social cognition) has been hypothesised to be dependent on a variety of factors: the capacity to understand emotions both in self and others, interpreting people's desires and intentions, the ability to regulate behaviour and be flexible in social interactions, and the competence to execute social behaviours and self-care skills or activities of daily living.[32] Earlier studies have shown that social cognition can be impaired early in the development of both Alzheimer's and frontotemporal dementia. Patients may suffer from maladjustment to the social environment and difficulty with sharing emotions and engaging spontaneously in social interactions. This results from superior temporal sulcus pathology affecting the ability to decode facial expressions and non-verbal communication.[13 32 33] We hypothesise that feelings of loneliness may subsequently be considered a manifestation of the deteriorating social skills that are seen as part of the personality change accompanying the process of dementia.[34] A third possible explanation for the association between feelings of loneliness and incident dementia is that these feelings are an indicator of unfavourable premorbid personality traits and behaviour. Recent findings suggest that more adaptive personality factors such as consciousness, extraversion and openness are inversely related to all-cause mortality. Persons

Table 5 Parsimonious model of factors predicting the development of dementia (logistic regression analysis)

	B	SE	Wald	df	Sig	Exp (B)
Feelings of loneliness	0.590	0.190	9.628	1	0.002	1.805
Increasing age	0.0543	0.094	33.323	1	0.000	1.722
MMSE	1.147	0.174	43.523	1	0.000	3.150
IADL disability	0.0546	0.195	7.846	1	0.005	1.727
CIND	1.077	0.306	12.354	1	0.000	2.935
Constant	−5.920	0.363	266.560	1	0.000	0.003

Variables removed during steps 1–8: participants living alone, not/no longer married, depression (including subthreshold depression), educational level, history of cerebrovascular disease, respiratory disease, p out 0.05, Nagelkerke R^2=0.194.
CIND, cognitive impairment no dementia; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination.

with these characteristics would be more likely to engage in healthy behaviours.[35] Feelings of loneliness could then be considered to be an expression of a frailty factor, signifying sensitivity to distress. Interestingly, distress proneness has been shown to be a risk factor for the development of Alzheimer's disease.[11] Feelings of loneliness may also (partly) represent a reaction to social isolation. In our study we corrected for social isolation. This reduced the association between feelings of loneliness and dementia, indicating that feelings of loneliness might be partly explained by the actual social situation of the individual. However, feelings of loneliness were not unique to persons living alone, as people who were married and receiving social support also experienced these feelings. In these persons also, feelings of loneliness were associated with dementia. Although few studies have examined the co-occurrence of (feelings of) loneliness with specific medical disorders, it is well known that depression and feelings of loneliness often co-occur and that loneliness appears to be a risk factor for poor physical health.[36] In our study we were able to control for depression. This only slightly reduced the association between feelings of loneliness and dementia, suggesting that this association is mostly independent of depression. Also, the fact that we found no interaction between feelings of loneliness and depression suggests that feelings of loneliness and depression are independent factors associated with dementia. Furthermore, we found that feelings of loneliness were a risk factor for depression at the 3-year follow-up. These results will be described elsewhere.

We found that not having adequate social support, believed to be a risk factor related to social isolation, actually showed the opposite effect in bivariate analysis. This association no longer existed in the multivariate model. To test the hypothesis that those receiving social support were in fact in poorer health and had more of the other risk factors for the development of dementia, we assessed physical conditions in participants with and without social support and examined interactions between social support and the other risk factors. Indeed, participants receiving social support had more ischaemic heart disease, cerebrovascular disease, respiratory disease, arthrosis/arthritis, diabetes, hypertension, cardiac arrhythmias, Parkinson's disease, depression, generalised anxiety disorder, CIND, dementia, ADL and IADL disabilities (all p values <0.02; data not shown). This means that poor health status may have masked the effect of not having social support in bivariate analysis.

A strength of the present study is that the dementia diagnosis was based on a reliable diagnostic and classification system with uniform evaluations, reducing the likelihood that diagnostic bias or imprecision affected the results. Unlike previous studies, this study distinguished between the subjective and qualitative characteristics of feelings of loneliness and the objective and quantitative characteristics of social isolation, which enabled a more thorough exploration of the differences between these two aspects. Further strengths are the cohort size, with a large number of participants experiencing feelings of loneliness, a representative 3-year incidence of clinical dementia comparable to other studies in this field,[6 8] and a comprehensive set of medical and social risk factors that in this combination are rarely, or not, available in other studies. Owing to the large sample size, we were able to adjust for all these factors. The fact that the study was performed in community-dwelling persons underlines the importance of our findings for public health.

Our study also has a number of limitations that should be mentioned. Despite the clinical assessment and the ability to distinguish between feelings of loneliness and social isolation, we were not able to use a more elaborate loneliness scale that could measure the severity and extent of loneliness and ascertain the structural aspects of social relationships (number of contacts and network size). The question 'Do you get help from family, neighbours or home support?' asks about the receipt of social support in an objective manner, but it cannot be ruled out that this assessment is confounded by subjective evaluations of the exchanges. However, at the time of the study, a more elaborate instrument was not available and the questionnaire used represented a reliable instrument for measuring social integration in terms of living alone and not being married.[6 8] Similar questions about social support to those used in our study, with questions also addressing subjective elements, are, however, also integrated into the present frequently used instruments for (social) loneliness: De Jong Gierveld and the UCLA loneliness scale.[37 38] There are also obvious advantages to using a short questionnaire when interviewing a large number of older people, and a single-question self-rating scale to measure loneliness has been widely used and is acceptable to research participants. It asks directly about loneliness and thus offers the possibility to give a personal, subjective account. Other loneliness scales are more indirect in asking about personal experience, as the questions are related to social networks and the availability of relationships. Although a single question or simple scale has been found to be more adaptable to performing research in older persons,[39 40] this simplicity also has disadvantages. For example, questions addressing feelings of loneliness require an understanding of the concept of loneliness by the participants, which may vary according to cultural background and identity.[39] A second consideration is that we did not have information on the history of participants concerning feelings of loneliness, whether these feelings had developed recently or whether they were part of an enduring condition or personality trait. Third, data on medical conditions were collected by means of a structured interview performed by trained and supervised interviewers. However, patients' self-report data on chronic diseases and conditions have been shown to be accurate and reliable.[41] A fourth possible limitation is that our definition of social isolation may be vulnerable to bias by depression. Although a factual account of a person's living situation and marital status is probably not affected by depression status, it is known that depressed persons overemphasise their actual isolation.[42] However, we found no interaction between feeling lonely and depressive symptoms at different severity levels at baseline. We did find that depression was more prevalent in persons who were receiving social support, but there was no interaction between depression and social support in both bivariate and multivariate analysis. A fifth limitation is that the response rate at follow-up was affected by the fact that 16.2% of subjects had died between assessments. Still, we believe it is unlikely that associations between feelings of loneliness and an untoward prognosis would have been less pronounced in subjects who had died. In a recent paper, we showed that feelings of loneliness are also associated with excess mortality,[43] and cognitive decline is one of the pathways to an earlier death. Another shortcoming of our study is that we were not able to control for apathy, as social isolation and loneliness may be associated with apathy.[44] Also, the prevalence of CIND in our study is relatively low, but similar prevalences have been found in other studies applying a narrow case definition for CIND.[45] This appears to be in contrast with prevalences of MMSE scores of 22–30 of 10.0% and of MMSE scores lower than 21 of 1.1%. The discrepancy between these MMSE scores and the relatively low prevalence of CIND can be explained by other factors known to determine MMSE scores such as

health-related factors, psychological functioning, age and educational level.[46–48] As the GMS AGECAT is an instrument with a higher sensitivity for detecting dementia than the MMSE, which measures general cognitive decline associated with various factors, we decided to apply GMS AGECAT and not the MMSE to exclude persons with dementia. Lastly, as our study is performed in a predominantly Caucasian population, we do not know to what extent our findings are generalisable to non-Caucasian populations.

In conclusion, feelings of loneliness were associated with development of dementia even when objective indicators of social isolation and other covariates were controlled for. Neither social isolation nor depression could account for this association, suggesting that other mechanisms may be involved. Further research is needed to investigate whether cognitive deterioration and dementia are a consequence of feelings of loneliness or whether feelings of loneliness are a behavioural reaction to diminished cognition. In order to develop a better understanding of these feelings, we need to know whether they are a signal of a prodromal stage of dementia or a direct result of neurodegenerative pathology affecting social skills or whether feelings of loneliness are an indicator of vulnerable personality, personality change or other frailty factors.

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