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Author: Hegeman, Annette

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Chapter 6

Loneliness and cardiovascular disease and the role of late-life depression

J.M. Hegeman*

N. Schutter*

H.C. Comijs

T.J. Holwerda

J. Dekker

M.L. Stek

R.C. van der Mast

Submitted

* These authors contributed equally as shared first authors

Abstract

Objective

Loneliness and depression have a strong reciprocal influence and both predict adverse health outcomes. In contrast to depression, little is known about the relation between loneliness and cardiovascular disease. This study examines the association between loneliness and cardiovascular disease in depressed and non-depressed older males and females.

Methods

Cross-sectional data of 477 depressed and non-depressed persons in the Netherlands Study of Depressed Older Persons (NESDO) were used. Logistic regression analysis was performed to examine the relation between loneliness and cardiovascular disease. Depression was added to the fully adjusted regression model to examine whether depression is an explanatory factor in the relation between loneliness and cardiovascular disease. Interaction terms were introduced in the regression model to investigate whether depressed and non-depressed males and females differed in their association between loneliness and cardiovascular disease.

Results

Loneliness and cardiovascular disease were not associated in the total group depressed and non-depressed persons after adjustment for confounders. No significant interaction term was found for loneliness and depression in their relation to cardiovascular disease. The interaction term between gender and loneliness (dichotomous: $p=0.005$; continuous: $p=0.003$) yielded a significant association with cardiovascular disease. Subsequent stratification revealed an association between loneliness and cardiovascular disease in females (continuous: odds ratio [OR]=1.13, 95% confidence interval [CI] 1.06-1.21, $p<0.001$; dichotomous: OR=2.64, 95% CI 1.50-4.65, $p=0.001$), but not in males. The association remained significant after adjustment for confounders, but it lost significance after adding depression in the model.

Conclusion

Loneliness and cardiovascular disease were associated only in females, but the presence of depression explained this association.

Introduction

Loneliness is a psychological experience that results from a lack of belonging.¹ It is considered to be an expression of negative feelings due to missing relationships.¹ Not only is loneliness one of the main indicators of social and mental wellbeing,^{1,2} it is also related to increased morbidity and mortality in later life.³⁻⁵ In both middle-aged and older persons, loneliness has been associated with higher blood pressure.⁶⁻⁹ Also, some lonely persons are more likely to be obese and to suffer from a metabolic syndrome.^{10,11} However, the mechanisms of negative health outcomes in relation to loneliness are largely unknown. It is possible that lifestyle factors (e.g. smoking, overweight, and low physical activity) and biological mechanisms (e.g. stress-induced endocrine and immune responses) play a role.^{11,12} As these lifestyle factors are risk factors for cardiovascular disease it is conceivable that, in the presence of loneliness, a risk profile for cardiovascular disease is more often present and, therefore, cardiovascular diseases may partly explain the adverse health outcome of loneliness. However, although the association between loneliness and cardiovascular diseases has rarely been examined,¹³ an association has been reported between loneliness and incident coronary heart disease in females, but not in males.¹⁴

Lonely older people often suffer from depressive symptoms, and loneliness and depression have a strong reciprocal influence in middle-aged and older persons.¹⁵⁻¹⁷ Moreover, a two-fold mortality risk was found in depressed older persons when loneliness was present.¹⁸ In contrast to loneliness, it is known that depression and cardiovascular diseases are closely related.¹⁹⁻²³ For instance, major depressive disorder is an independent risk factor for mortality following myocardial infarction.²⁰ In middle-aged and older females, recurrent major depressive disorder was found to be a predictor for cardiovascular disease.²⁴ Depression is also related to incident stroke²⁵ and to peripheral artery disease²⁶. Consequently, the strong increase in mortality found in the co-occurrence of loneliness and depression might be explained by cardiovascular disease.¹⁸

This study investigates whether loneliness is associated with cardiovascular disease, in both depressed and non-depressed older males and females. More specifically, we explore whether depression explains the association between loneliness and cardiovascular disease, and whether such an association differs between depressed and non-depressed older males and females.

Methods

Participants

For this study, data were used from the baseline assessment of the Netherlands Study of Depressed Older Persons (NESDO). The NESDO started in 2007 and is an ongoing prospective cohort study on the determinants, long-term course and consequences of depressive disorders among older people aged ≥ 60 years recruited from different regions (e.g. urban and rural areas) in the Netherlands.²⁷ In the baseline NESDO sample 378 depressed and 132 non-depressed older persons were included from mental healthcare and primary healthcare settings to create a sample reflecting all different stages of depression. Excluded were persons with a primary diagnosis of dementia according to the clinician, a psychotic or bipolar disorder, a Mini Mental State Examination score (MMSE) ≤ 18 (out of 30 points), or insufficient command of the Dutch language. Non-depressed controls were recruited from primary healthcare settings; inclusion criteria for the controls were: no lifetime depression, no dementia or other serious psychiatric condition, and good command of the Dutch language. The study protocol of NESDO was centrally approved by the Ethical Review Board of the VUMC and also by the local ethical review boards of each participating center.²⁷ During a four-hour baseline assessment (including written questionnaires, interviews, a medical examination, a cognitive computer task and the collection of blood and saliva samples), a wide range of information was gathered about health outcomes and demographic, psychosocial, clinical, biological and genetic determinants.

Measurements

Loneliness

Loneliness was measured with the original 11-item De Jong Gierveld loneliness scale. The De Jong Gierveld loneliness scale is a valid instrument to measure overall loneliness.^{28,29} Items in the De Jong Gierveld loneliness scale are scored on a 5-point scale. In this study, items were rescored into a dichotomous value: responses indicating loneliness are assigned a score of 1 and responses indicating no loneliness are assigned a score of 0. The maximum total score of the De Jong Gierveld loneliness scale is 11, with a cut-off score of 3 to distinguish between lonely and not lonely individuals.²⁸

Cardiovascular disease

The presence of cardiovascular disease was assessed using a self-report questionnaire. That is, participants were asked whether they have, or have ever had angina, a heart infarct, cardiac arrhythmia, heart failure, any other heart condition (e.g. valvular heart disease), a stroke, or pain in the calves during walking. The use of a self-report questionnaire to assess

the presence of chronic somatic diseases was found accurate compared to information gathered from a general practitioner, with the exception of self-reported peripheral vascular disease.³⁰ Therefore, self-reported pain in the calves was combined with the ankle-brachial index (ABI) to more accurately assess the presence of peripheral vascular disease (PVD).^{31,32} The ABI has shown to be effective in measuring PVD and is defined as the ratio of the ankle and brachial blood pressure that predicts PVD if the score is ≤ 0.9 .³² In addition, including information about the use of medication did not further improve the accuracy of self-reported information on the presence of somatic illnesses.³³

Depression

The Composite International Diagnostic Interview (CIDI; WHO version 2.1) was used to assess the presence of a depressive disorder (major depression, dysthymia and minor depression) according to the DSM-IV-Classification within six months before the baseline assessment.

Covariates

Demographic characteristics such as age, gender, years of education and partner status were collected using standard questions. Social network was measured with the Close Person Inventory that counts the number of meaningful relationships (e.g. friends and relatives) and was dichotomized using a cut-off of 6 persons.³⁴ Current smoking status was assessed by simple questions. The Alcohol Use Disorders Identification Test (AUDIT) was used to assess alcohol use, defined as the amount of glasses a day.³⁵ Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) that calculates the total metabolic equivalent of task (MET) minutes a week.³⁶ MET minutes represent the energy cost for daily activities compared to the energy cost for a person at rest.

Statistical analyses

T-test and chi-square tests were used to detect differences between the lonely and non-lonely participants with respect to depression status, cardiovascular disease and all covariates. For non-normally distributed variables, Mann-Whitney tests were used. Multiple imputation techniques were applied due to missing values for the covariates social network size (1.6% missing) and physical activity (17.6% missing). To detect relevant confounders, logistic regression analyses were performed in which all potential confounders were entered one by one in the models to examine whether a $\geq 10\%$ change occurred in the odds ratio (OR) of the association between loneliness and cardiovascular disease.

Logistic regression analysis was used to examine the association between loneliness as dichotomous determinant and the presence of cardiovascular disease as outcome variable. The model was adjusted for relevant confounders. In the fully adjusted model,

depression was introduced, to investigate whether depression was an explanatory factor in the association between loneliness and cardiovascular disease. Depression was considered an explanatory factor if a $\geq 10\%$ change occurred in the OR of the association between loneliness and cardiovascular disease. Next, the interaction term between loneliness and depression was introduced in the fully adjusted model to examine whether the association between loneliness and cardiovascular disease was different for depressed compared to non-depressed participants. In case this interaction was significant ($p < 0.05$), analyses were repeated for the two subgroups (depressed and non-depressed) separately. We also introduced an interaction term for loneliness and gender, to explore whether there is a gender-specific association between loneliness and cardiovascular disease. In case a significant interaction term was found, regression analyses were repeated in males and females separately. Further, all regression analyses were repeated with overall loneliness severity as a continuous determinant.

Results

Loneliness scores were available for 477 participants (6.5% missing). Persons with missing data were not different from included persons with respect to mean age (70.9 v. 70.6 years, $p=0.82$), female gender (63.6% v. 65.0%, $p=0.88$), partner status (married or has a partner: 48.5% v. 58.9%, $p=0.24$), physical activity (total MET minutes/week: 2578 v. 2665, $p=0.88$), and the presence of depression (81.8% v. 73.6%, $p=0.30$) or cardiovascular disease (33.3% v. 27.9%, $p=0.51$). Table 1 summarizes the sociodemographic and clinical characteristics of the study sample according to their loneliness status. The mean age (SD) of the total study sample was 70.6 (7.3) years and 64.9% was female. Lonely participants were significantly older, were more often males and without a partner, had fewer years of education and a smaller social network, and were more often depressed. Furthermore, lonely participants had more often a cardiovascular disease, and were more often smokers and less often engaged in physical exercise. However, lonely participants drank less alcohol.

Logistic regression analyses in which all potential confounders were entered one by one in the models revealed that partner status, physical activity level and social network size were confounders in the association between loneliness and cardiovascular disease. Therefore, these variables were introduced as covariates in the subsequent analyses. We also included age as a covariate to adjust for age-effects.

We performed logistic regression analyses with the presence of cardiovascular disease as outcome. First, we ran this analysis with loneliness as a dichotomous variable and adjusted for the confounders mentioned above. These analyses showed no significant association

Table 1. Characteristics of the study population (n=477).

	Lonely (n=289)	Not lonely (n=188)	p-value*
Age, mean (SD)	71 (7.2)	70 (7.3)	<0.001
Female gender, n (%)	186 (64.4)	124 (66.0)	<0.001
Years of education, mean (SD)	10.4 (3.5)	11.7 (3.6)	<0.001
Depressive disorder in past 6 months, n (%)	265 (91.7)	86 (46.7)	<0.001
Partnerstatus, n (%) with partner	138 (47.8)	143 (76.1)	<0.001
Social network, n (%)			<0.001
< 6	180 (62.7)	61 (32.6)	0.001
≥ 6	107 (37.3)	126 (67.4)	<0.001
Current smoker, n (%)	75 (26.0)	25 (13.4)	<0.001
Alcohol use: AUDIT score (SD)	2.44 (3.4)	3.48 (3.1)	0.032
Physical activity MET-min./week (SD)	2392 (2511)	3099 (2866)	<0.001
Cardiovascular disease, n (%)	91 (31.5)	42 (22.5)	0.032

* Normally distributed variables were tested with t-tests (continuous variables) or chi-square tests (categorical) and non-normally distributed variables were tested with Mann-Whitney tests.
Abbreviations: SD, standard deviation; AUDIT, Alcohol Use Disorders Identification Test; MET, metabolic equivalent of task.

Table 2. Association between loneliness (dichotomous) and cardiovascular disease.

	OR (95% CI)	p-value
<i>Crude</i>		
Loneliness	1.59 (1.04-2.42)	0.03
<i>Adjusted</i>		
Loneliness*	1.27 (0.80-2.03)	0.32
Loneliness**	1.16 (0.69-1.93)	0.58
Loneliness x depression**	0.74 (0.23-2.36)	0.61

*Adjusted for age, partner status, physical activity, social network size.
**Adjusted for the above mentioned variables, plus depression.

between loneliness and cardiovascular disease (Table 2). Next, we added the interaction term between depression and loneliness to the fully adjusted model. However, this interaction terms was not statistically significant (Table 2). These logistic regression analyses were repeated with loneliness as a continuous variable. Again, no significant association between loneliness and cardiovascular disease was found after adjustment for confounders (Table 3). Also the interaction term between depression and loneliness showed no significant association with cardiovascular disease ($p=0.09$).

The interaction term between gender and loneliness yielded a significant association for loneliness as dichotomous variable (OR=3.61, 95% confidence interval [CI] 1.47-8.83, $p=0.005$) and for loneliness as a continuous variable (OR=1.20, 95% CI 1.06-1.35, $p=0.003$). Therefore, we repeated the logistic regression analyses in the males and females separately (Table 4). A significant association between loneliness (dichotomous and continuous) and cardiovascular disease was found in females, but not in males. After adjustment for confounders, the association remained significant for loneliness as a dichotomous and continuous variable, but it lost significance when depression was added to the model. Further, in females, a significant interaction term of depression and loneliness was found with loneliness as a continuous variable ($p=0.03$), but not with loneliness as a dichotomous variable. Stratification by depression did not reveal significant associations between loneliness as a continuous variable and cardiovascular disease in the depressed (OR=1.04, 95% CI 0.95-1.13, $p=0.46$) and non-depressed (OR=1.31, 95% CI 0.96-1.79, $p=0.09$) females.

Table 3. Association between loneliness (continuous) and cardiovascular disease.

	OR (95% CI)	p-value
<i>Crude</i>		
Loneliness	1.07 (1.01-1.13)	0.02
<i>Adjusted</i>		
Loneliness*	1.04 (0.98-1.10)	0.25
Loneliness**	1.03 (0.96-1.10)	0.48
Loneliness x depression*	0.85 (0.71-1.03)	0.09
*Adjusted for age, partner status, physical activity, social network size.		
**Adjusted for the above mentioned variables, plus depression.		

Table 4. Association of loneliness (dichotomous and continuous) and cardiovascular disease in males and females.

	Males (n=167)		Females (n=309)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
<i>Crude</i>				
Loneliness (dichotomous)	0.96 (0.88-1.05)	0.38	2.64 (1.50-4.65)	0.001
<i>Adjusted</i>				
Loneliness *	0.93 (0.83-1.03)	0.18	1.96 (1.05-3.63)	0.03
Loneliness **	0.91 (0.81-1.03)	0.13	1.75 (0.88-3.50)	0.11
<i>Crude</i>				
Loneliness (continuous)	0.71 (0.36-1.40)	0.33	1.13 (1.06-1.21)	<0.001
<i>Adjusted</i>				
Loneliness *	0.62 (0.29-1.31)	0.21	1.10 (1.01-1.18)	0.02
Loneliness **	0.57 (0.26-1.27)	0.17	1.08 (0.99-1.18)	0.08
*Adjusted for age, partner status, physical activity, social network size.				
** Adjusted for the above mentioned variables, plus depression.				

Discussion

In this study, the relation between loneliness and cardiovascular disease was examined in a depressed and non-depressed older population. Significant associations were found between loneliness and cardiovascular disease. However, when relevant confounders were added to the model, the association between loneliness and cardiovascular disease did not remain significant. This suggests that multiple factors (e.g. physical activity, social network size, partner status) that co-occur with loneliness, but not loneliness itself, influence the presence of cardiovascular disease. Nevertheless, in females only, the association between loneliness and cardiovascular disease remained significant after adjustment for relevant confounders, but it lost significance after adjustment for depression. In conclusion, a significant association between loneliness and cardiovascular disease was only found in females, but the presence of depression explained this association.

Our results are not in line with other studies examining the association between loneliness and cardiovascular disease, with the exception of one study.³⁷ In this latter study,

no obvious association between coronary insufficiency and feelings of loneliness was found in a population aged 70-90 years.³⁸ To our knowledge, few studies found loneliness to be associated with cardiovascular disease^{13,14,38} and none of these studies considered the potential explanatory role of depression. For instance, one study found greater loneliness to be associated with increased probability of having a coronary condition, even after adjustment for lifestyle factors;¹³ however, that study did not correct for a diagnosis of depression. Another study examined incident coronary heart disease in a longitudinal study of a community sample of male and females and found loneliness to be associated with an increased risk of incident coronary heart disease among females.¹⁴ Models were adjusted for various confounders but not for the diagnosis of depression. Furthermore, in contrast to our study, loneliness was assessed with only one item from the Center for Epidemiologic Studies of Depression scale. Since the mean age in this latter study was 44 years, it is not directly comparable to our study with a much older population. In fact, we did find an association between loneliness and cardiovascular disease in females, and not in males. However, in our study, we found that the presence of depression explained this association. Another study analyzed the relationship between loneliness and cardiovascular mortality and found a feeling of loneliness to be associated with cardiovascular mortality, especially among males.³⁸ However, they used a single question to assess loneliness, and depression was not assessed in their study. In summary, the present study shows that when examining the association between loneliness and cardiovascular disease in older adults, it is important to adjust for the presence of depression, especially in females. The fact that other studies did not take the presence of depression into account, might in part explain the difference in the findings.

In contrast to loneliness, the association between depression and cardiovascular disease has been confirmed more often.²⁰⁻²² Importantly, these studies did not take into account the strong mutual relation between depression and loneliness. In our study, however, there was no evidence that loneliness might explain the previously found association between depression and cardiovascular disease. Therefore, our findings do not support the hypothesis that cardiovascular disease might explain the previously found increased mortality and morbidity associated with loneliness. This is in line with the results of others: for example, a prospective cohort study found no decline of health and longevity in lonely older persons.³⁹ Other studies found that social isolation, but not loneliness, was associated with mortality.^{3,40}

A major strength of the present study is a study population recruited from different healthcare settings that consisted of depressed and non-depressed older persons. This allowed to rule out the possibility of a confounded relation between loneliness and cardiovascular disease based on depression. To our knowledge, no other study has examined loneliness and formally diagnosed depression together in relation to cardiovascular disease.

The present study also has some limitations. First, it was not possible to include the length of time that loneliness was experienced because this information was not available. However, it is possible that only loneliness experienced on the long-term predicts cardiovascular disease. This could imply that a lack of such an association in our study might be due to a shorter duration of loneliness in our participants; longitudinal research is needed to confirm this. Secondly, some participants could not be included due to missing values on the loneliness scale. However, because no differences were found in relevant variables between persons with missing values on the loneliness scale and included persons, it is unlikely that our results are biased due to selection.

In conclusion, until now there is lack of agreement among studies regarding the association between loneliness, cardiovascular risk factors, cardiovascular disease and mortality. Our results suggest that loneliness in its own right is not related to cardiovascular disease in depressed and non-depressed older adults. Apparently, the higher morbidity and mortality that is associated with loneliness do not seem to originate in an association with cardiovascular disease.^{3,4} Depression and other factors (e.g. partner status, physical activity level and social network size) associated with loneliness may be involved in the association with morbidity and mortality.

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