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Loneliness, social network size, and mortality in older adults and the role of cortisol

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CONTACT Natasja Schutter

ABSTRACT

Background: Loneliness and social isolation have both been found to be associated with increased mortality in previous studies. One potential underlying mechanism is via the hypothalamic-pituitary-adrenal axis.

Objective: This study aimed to examine the association between social network size and cortisol, to analyze the associations between both loneliness and social network size and mortality, and to examine to what extent the associations between network size and/or loneliness and mortality is mediated by cortisol.

Design: The study group consisted of 443 depressed and non-depressed participants of the Netherlands Study of Depression in the Elderly (NESDO). Cross-sectional analysis of the association between social network size and cortisol measures was followed by a survival analysis of the associations between both social network size and loneliness and mortality.

Results: There were no significant associations between social network size and cortisol measures. Loneliness and small social network size were not associated with mortality. Age and partner status were more important predictors of mortality.

Conclusion: As people grow older the variety of factors that influence mortality risk increases, diminishing the effect of a single factor. Prevention of early morbidity and mortality in older adults should be tailored to specific needs and risks, instead of aiming at one specific factor.

Introduction

The prevalence of loneliness and social isolation increases with age as a result of deteriorating health, increasing disability, widowhood and decreasing social integration (De Jong Gierveld & Havens, 2004; Fokkema, De Jong Gierveld, & Dykstra, 2012; Jylhä, 2004). It varies from 6% to 25% in various European countries (Fokkema et al., 2012) to 35%–39% in Swedish and Finnish studies (Routasalo, Savikko, Tilvis, Strandberg, & Pitkalä, 2006), showing percentages between 20% and 40% in all Western countries (Luo, Hawkley, Waite, & Cacioppo, 2012).

Loneliness can be defined as the subjective experience of the discrepancy between the desired and actual amount or intensity of social contacts (De Jong Gierveld & Van Tilburg, 2006; Hawkley & Cacioppo, 2010), whereas social isolation is an objective indicator that reflects a small social network size (Luanaigh & Lawlor, 2008; Routasalo et al., 2006; Shankar, McMunn, Banks, & Steptoe, 2011; Steptoe, Shankar, Demakakos, & Wardle, 2013), the absence of a spouse, low frequency of social contacts, or lack of participation in social groups (Cacioppo, Cacioppo, Capitanio, & Cole, 2015). Both loneliness and social isolation have been found to be associated with higher mortality (Berkman, 1995; Holwerda et al., 2012; Luo et al., 2012; Olsen, Olsen, Gunner-Svensson, & Waldstrom, 1991; Patterson & Veenstra, 2010; Penninx et al., 1997; Perissinotto, Stijacic Cenzers, & Covinsky, 2012; Shiovitz-Ezra & Ayalon, 2010).

The underlying causal mechanisms of the effects of loneliness and social isolation on mortality are not yet clear. Research has focused on dysregulation of the hypothalamic-pituitary-adrenal axis as a putative mediator in the association between loneliness and social isolation and higher mortality, since both high cortisol levels (Aubert, Folly, Mancinetti, Hayoz, & Donze, 2016; Hammer et al., 2016; Zurfluh et al., 2018) and low cortisol levels (Maripuu, Wikgren, Karling, Adolfsson, & Norrback, 2016) are associated with higher mortality. In older adults, loneliness has been found to be associated with a higher cortisol awakening response (Adam, Hawkley, & Kudielka, 2006; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004) but also with diminished cortisol output (Schutter et al., 2017). Social isolation in older adults has been found to be associated with higher nighttime cortisol levels and a flatter diurnal slope (Stafford, Gardner, Kumari, Kuh, & Ben-Shlomo, 2013). In middle-aged adults, social isolation was associated with a larger cortisol awakening response and greater cortisol output (Grant, Hamer, & Steptoe, 2009).
Social isolation, loneliness and depression are closely related (Cacioppo, Hughes, & Waite, 2006; Santini et al., 2020; Taylor, Taylor, Nguyen, & Chatters, 2018). In late-life depression, dysregulation of the hypothalamic-pituitary-adrenal axis has been a fairly consistent finding (Belvederi Murri et al., 2014; Rhebergen et al., 2015). Therefore, when investigating cortisol levels in lonely or socially isolated persons, it is important to take depression into account.

The Netherlands Study of Depression in the Elderly (NESDO) was designed to examine the determinants and course of depression in older adults (Comijs et al., 2011). Various covariates have been measured, among which were loneliness, social network, cortisol in saliva, and data about psychiatric and somatic comorbidity as well as mortality. For this reason, NESDO offers an excellent possibility to examine loneliness and social network size in depressed and non-depressed older adults and their relationships with both cortisol and mortality.

The association between loneliness and cortisol has previously been studied in NESDO (Schutter et al., 2017). The results showed that loneliness was associated with diminished cortisol output and diminished dexamethasone suppression (Schutter et al., 2017). Since we were not only interested in the subjective experience of social relationships (i.e. loneliness), but also in the objective aspects, we wanted to add to this research by investigating the association between social network size and cortisol. Social network size is an often-used measure of objective social isolation (de Brito, Nunes, Corona, da Silva Alexandre, & de Oliveira Duarte, 2017; Ellwardt, Van Tilburg, Aartsen, Wittek, & Steverink, 2015; McLaughlin, Leung, Almeida, & Dobson, 2011). With respect to the associations with mortality, we were again interested in both the subjective and the objective aspects of social isolation. Therefore, we investigated loneliness as a subjective measure, and social network size as an objective measure, in relation to mortality.

Our research questions were: 1) Is a small social network associated with lower cortisol levels in older adults? 2) Are loneliness and small social network at baseline associated with higher mortality at six years follow-up? 3) Is the association between loneliness and/or small social network and mortality mediated by cortisol levels?

**Methods**

**Study sample**

Participants were derived from the NESDO-study. Detailed information about study design, recruitment and methods was described elsewhere (Comijs et al., 2011). In short, depressed participants were recruited from both general health practices and mental health institutions. The non-depressed participants were recruited from general health practices and they were included only when there was no previous lifetime diagnosis of depression. Exclusion criteria included Mini Mental State Examination (MMSE)-score of 18 or less (out of a total of 30), the presence of a dementia diagnosis, the presence of a severe psychiatric disorder other than depression, and not being fluent in the Dutch language. The complete study population consisted of 510 participants: 378 depressed and 132 non-depressed adults aged 60-93 years. Because of missing values on cortisol measures, our study population consisted of 443 participants. Additionally, 15 persons had missing values on loneliness. There were no additional missings on network size. Participants with missing values on cortisol measures did not differ significantly from participants without missing values with respect to social network size and loneliness. A diagnosis of depression included a 6-month diagnosis of a Major Depressive Disorder (MDD) (95%) and/or a 6-month dysthymic disorder (26.5%), or a minor depression (5%) according to DSM-IV-TR criteria (APA 2000). The ethical review boards of participating study sites approved of the research protocol and all respondents provided written informed consent.

**Measurements**

**Cortisol**

Cortisol was obtained from saliva samples. After the initial interview, participants were instructed to collect saliva samples at home on two consecutive days at the following times: at the time of awakening (T1), 30 min post-awakening (T2), 45 min post-awakening (T3), 60 min post-awakening (T4) and at 22:00 h (T5). Additionally, dexamethasone suppression was calculated from a morning sample at awakening (T6) after ingestion of 0.5 mg of dexamethasone the night before. The Dexamethasone Suppression Test (DST) is a measure of HPA-axis regulation and normally shows a decrease of morning cortisol concentrations due to inhibition of adrenocorticotropic hormone (ACTH) secretion after ingestion of dexamethasone the night before (APA 1987). After restoring them in a tube, the salivettes were labeled with the date and time. Participants were instructed to send all six salivettes to the research center by mail. After receipt, all salivettes were centrifuged at 2000g for 10 min, aliquoted and stored at −80°C. Cortisol analysis was performed by competitive electrochemiluminescence immunoassay (E170 Roche, Switzerland). The functional detection limit was 2.5 nmol/l and the intra- and inter-assay variability coefficients in the measuring range were less than 10% (Rhebergen et al., 2015).

**Cortisol awakening response (CAR)**. Using the four saliva samples taken in the first hour after awakening (T1 through T4), the areas under the curve with respect to the increase (AUCi) and with respect to the ground (AUCg) were calculated using Pruessner’s formulas (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The AUCg and AUCi are different measures for cortisol secretion, where AUCg is an estimate of the total cortisol secretion over the first hour after awakening, and AUCi represents the dynamics of the cortisol awakening response (CAR), emphasizing changes over time after awakening (see also Rhebergen et al., 2015). When only one cortisol measure was missing, the missing value was imputed using linear mixed models analyses including information on the three available cortisol levels, sex, age, awakening time and smoking status (Rhebergen et al., 2015).

**Evening cortisol and diurnal slope**. The diurnal slope was calculated by subtraction of the evening sample (T5) from the sample at awakening (T1), resulting in the decline in cortisol level during the day (Rhebergen et al., 2015). Adam and Kumari (2009) described a frequently used method for obtaining a diurnal slope by subtracting the wake-up
cortisol value from the one at bedtime, divided by the total time awake. Since we did not measure the total time awake, we were not able to calculate the diurnal slope in this way.

**Dexamethasone suppression test (DST).** In participants who had ingested 0.5 mg of dexamethasone at nighttime and taken a saliva sample at awakening the next morning, we calculated the dexamethasone suppression ratio by dividing the cortisol value at awakening on day 1 (T1) by the cortisol value at awakening the day after dexamethasone ingestion (T6) (Rhebergen et al., 2015).

**Social network size**

Social network size was measured with the Close Persons Questionnaire (CPQ) (Stansfeld & Marmot, 1992). This questionnaire measures the amount of contacts in the social network, as well as some qualitative aspects such as emotional support, confiding, and practical and negative aspects of support. It has been tested in a large epidemiological survey and validated by interview (Stansfeld & Marmot, 1992). In this study we only used the size of the network. Network size was divided into six categories: 0–1 contacts, 2–5, 6–10, 11–15, 16–20 and more than 20 contacts. Alternatively, network size was divided into two groups: five persons or less, versus more than five persons.

**Loneliness**

Loneliness was assessed using the De Jong Gierveld Loneliness Scale (De Jong Gierveld & Kamphuis, 1985). This is an 11-item questionnaire that was developed for use in scientific surveys. It was found to be a reliable and valid instrument (Van Tilburg & Jong Gierveld, 1999). Every item can be answered on a 5-point scale. The answers are then dichotomized, leading to a score between 0 and 11. The cut-off score for loneliness is 3 and the cut-off score for severe loneliness is 9 (Van Tilburg & Jong Gierveld, 1999).

**Mortality**

Information about mortality at 6 years follow-up was derived from the interviews. In each wave, response numbers were registered, including the reason for non-response.

**Covariates**

Because in previous studies associations were found between cortisol values and various socio-demographic, biological, lifestyle and sampling factors, it is important to control for these factors (Rhebergen et al., 2015; Vreeburg et al., 2009).

Sociodemographic factors included age, sex, partner status, and years of education.

**Clinical characteristics.** A depression diagnosis included a primary diagnosis of major depression, dysthymia or minor depression according to DSM-IV-TR criteria in the past 6 months and was assessed with the Composite International Diagnostic Interview (CIDI) (WHO 1990). The CIDI is a structured clinical interview that is designed for use in research settings. It has been proven to possess high validity and reliability (Wittchen, 1994; Wittchen et al. 1991).

The severity of depressive symptoms in the past week was measured using the 30-item Inventory of Depressive Symptomatology – Self Report version (IDS-SR). The IDS-SR is a valid and reliable instrument, also for use in older persons (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996).

Health characteristics included the number of chronic diseases, which were assessed by means of a self-report questionnaire that has previously been used in the Longitudinal Aging Study Amsterdam (Kriegsman, Penninx, Van Eijk, Boeke, & Deeg, 1996). Participants were asked whether they currently or previously had any of the following chronic diseases: cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, COPD, arthritis or cancer, or any other disease.

Lifestyle characteristics. These included Body Mass Index (BMI), smoking status (no smoker or current smoker), alcohol use as measured with the Alcohol Use Disorders Identification Test (AUDIT) (Babor, Kranzler, & Lauerman, 1989), and physical activity (measured with the International Physical Activity Questionnaire (IPAQ)) in metabolic equivalent of task (MET)-minutes (Craig et al., 2003).

**Sampling factors.** Cortisol sampling factors consisted of time of awakening and season on the first sampling day. Season was categorized by months with less daylight (October–February) and more daylight (March–September) (Rhebergen et al., 2015).

**Statistical analyses**

Social network was analyzed in 6 categories and as a dichotomous measure. Previous research used a ‘social isolation index’ (Grant et al., 2009) or a dichotomous measure (Stafford et al., 2013). In previous research investigating the association between network size and mortality there is no agreement on how to include social network size. Some authors used actual network size, others divided network size in categories, tertiles or two groups. Because of this lack of agreement we analyzed network size both in categories and as a dichotomous measure.

Participants were compared according to dichotomous social network size using Student’s t test for continuous variables, Chi square statistics for dichotomous variables and Mann–Whitney U-tests for non-normally distributed variables.

When cortisol values were normally distributed, we investigated the association with social network size (in categories and dichotomous) using multivariate linear regression analyses. In case of non-normal distribution we divided the cortisol measures in tertiles and used multinominal logistic regression analyses. Covariates were considered confounders when they changed B more than 10 percent (Twisk, 2010).

In order to account for the effects of depression on cortisol levels, we investigated whether the association between social network size and cortisol was different for depressed compared to non-depressed participants by analyzing the interaction between social network size and depression severity.

In the second part of the study, the study participants were compared according to mortality status using
Table 1. Characteristics of the study population (n = 443).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Network ≤ 5 persons (n = 231)</th>
<th>Network &gt; 5 persons (n = 212)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>70 (7.2)</td>
<td>70 (7.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female (%)</td>
<td>140 (61)</td>
<td>141 (67)</td>
<td>0.20</td>
</tr>
<tr>
<td>Partner status (% with partner)</td>
<td>136 (59)</td>
<td>133 (63)</td>
<td>0.41</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>11.0 (3.7)</td>
<td>11.2 (3.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Depression diagnosis (%)</td>
<td>200 (87)</td>
<td>126 (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total IDS scores, mean (SD)</td>
<td>28.2 (14.5)</td>
<td>18.9 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of somatic illnesses, mean (SD)</td>
<td>2.1 (1.4)</td>
<td>1.8 (1.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.4 (4.6)</td>
<td>26.7 (4.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>57 (25)</td>
<td>36 (17)</td>
<td>0.05</td>
</tr>
<tr>
<td>Physical activity MET-min/week (SD)</td>
<td>2438 (2640)</td>
<td>3005 (2749)</td>
<td>0.04</td>
</tr>
<tr>
<td>AUDIT score, mean (SD)</td>
<td>2.8 (3.5)</td>
<td>3.1 (3.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Loneliness scores, mean (SD)</td>
<td>6.7 (3.6)</td>
<td>3.8 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sampling factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of awakening:</td>
<td>7:28 (1:08)</td>
<td>7:27 (0:55)</td>
<td>0.81</td>
</tr>
<tr>
<td>Total IDS scores, mean (SD)</td>
<td>149 (65)</td>
<td>138 (65)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cortisol values:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 median (IQ)</td>
<td>16.3 (11.2)</td>
<td>16.3 (10.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>AUCg, µg/dL/h median (IQ)</td>
<td>17.5 (10.7)</td>
<td>17.7 (9.4)</td>
<td>0.87</td>
</tr>
<tr>
<td>AUCi, µg/dL/h median (IQ)</td>
<td>–0.27 (8.7)</td>
<td>0.94 (8.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Diurnal slope median (IQ)</td>
<td>12.0 (10.9)</td>
<td>12.2 (10.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cortisol suppression ratio median (IQ)</td>
<td>2.7 (2.3)</td>
<td>2.6 (2.0)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

IDS, Inventory of Depressive Symptoms; BMI, body mass index; MET, metabolic equivalent of task; AUDIT, Alcohol Use Disorders Identification Test; AUCg, area under the curve with respect to the ground; AUCi, area under the curve with respect to the increase.

*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 U tests.

Table 2. Regression analyses for network size with cortisol measures as outcome.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>95%CI for B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>lnAUCg</td>
<td>0.02</td>
<td>–0.04–0.04</td>
<td>0.92</td>
</tr>
<tr>
<td>lnAUCg, network size × IDS-score</td>
<td>0.11</td>
<td>–0.24–0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>lnAUCi, network size × IDS-score</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Middle versus low T1  
High versus low T1

Student’s t test for continuous variables, Chi square statistics for dichotomous variables and Mann–Whitney U-tests for non-normally distributed variables. The associations between loneliness and mortality and between social network size and mortality were investigated using Cox Proportional Hazards analyses. Loneliness was analyzed both as a continuous variable and as a dichotomous variable; social network size was analyzed both in six categories and as a dichotomous variable. Interactions with depression status and sex were analyzed. A sensitivity analysis was added analyzing the associations with mortality in the depressed group only.

In the third part of the study, we planned to use an Accelerated Failure Time model (Burgos Ochoa et al., 2020; Gelfand, MacKinnon, DeRubeis, & Baraldi, 2016) to analyze the mediating effect of cortisol.

Results

Characteristics of the study population according to network size are shown in Table 1. The cortisol measures did not show a normal distribution. However, the natural logs of AUCi and AUCg were normally distributed (lnAUCi showed a skewness of −0.18 with a standard error of 0.14 and a kurtosis of −0.26 with a standard error of 0.36; lnAUCg showed a skewness of −0.18 with a standard error of 0.14 and a kurtosis of 0.17 with a standard error of 0.27). Hence, we used linear regression analyses for lnAUCi and lnAUCg and multinominal logistic regression analyses for T1, diurnal slope and DST in tertiles.

The results are shown in Table 2. Social network size was not significantly correlated with any of the cortisol measures. Repeating the analyses with social network size in two groups (with 5 persons as cut-off) did not change the outcomes. This was not different for depressed compared to non-depressed participants, as there were no interactions with severity of depressive symptoms.

Table 3 shows the characteristics of the study population according to mortality status. The deceased participants did not differ from the not deceased participants with regard to loneliness score and social network size. However, they did differ with respect to several known mortality risk factors such as age, partner status, number of somatic diseases, and physical activity.

Table 4 shows the results of the Cox Regression analyses. Neither loneliness, nor social network size was significantly associated with mortality. Age and partner status were far more important predictors of mortality. Number of chronic diseases, BMI, MET-minutes and AUDIT-score were no longer significant predictors when put into the model with age.
**Table 3.** Characteristics of the study population according to mortality status.

<table>
<thead>
<tr>
<th></th>
<th>Alive (n = 389)</th>
<th>Deceased (n = 54)</th>
<th>p value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>70 (7)</td>
<td>74 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>44 (65)</td>
<td>27 (51)</td>
<td>0.10</td>
</tr>
<tr>
<td>Partner status, n with partner (%)</td>
<td>248 (64)</td>
<td>21 (40)</td>
<td>0.002</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>11 (3.6)</td>
<td>11 (3.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Depression diagnosis, %</td>
<td>279 (72)</td>
<td>46 (87)</td>
<td>0.06</td>
</tr>
<tr>
<td>Total IDS scores, mean (SD)</td>
<td>23 (15)</td>
<td>27 (15)</td>
<td>0.12</td>
</tr>
<tr>
<td>No. of somatic illnesses, mean (SD)</td>
<td>1.9 (1.4)</td>
<td>2.5 (1.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26 (4.2)</td>
<td>27 (5.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>77 (20)</td>
<td>15 (28)</td>
<td>0.06</td>
</tr>
<tr>
<td>Physical activity MET-min/week (SD)</td>
<td>2693 (2747)</td>
<td>1941 (2712)</td>
<td>0.05</td>
</tr>
<tr>
<td>AUDIT score, mean (SD)</td>
<td>2.9 (3.3)</td>
<td>2.6 (3.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Loneliness score, mean (SD)</td>
<td>5.2 (3.7)</td>
<td>6.2 (3.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Social network, number of persons above 18:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1, n (%)</td>
<td>42 (11)</td>
<td>6 (11)</td>
<td>0.10</td>
</tr>
<tr>
<td>2–5, n (%)</td>
<td>157 (40)</td>
<td>26 (49)</td>
<td></td>
</tr>
<tr>
<td>6–10, n (%)</td>
<td>112 (29)</td>
<td>15 (28)</td>
<td></td>
</tr>
<tr>
<td>&gt;10, n (%)</td>
<td>78 (20)</td>
<td>6 (11)</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{IDS, Inventory of Depressive Symptoms; BMI, body mass index; MET, metabolic equivalent of task; AUDIT, Alcohol Use Disorders Identification Test.}\)

\(\text{aNormally distributed variables were tested with t tests (continuous variables) or chi-square tests (categorical) and non-normally distributed variables were tested with Mann–Whitney U tests.}\)

**Table 4.** Cox Regression Analyses.

<table>
<thead>
<tr>
<th></th>
<th>Chi square</th>
<th>HR</th>
<th>CI (95%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loneliness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1:</td>
<td>2.9</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Loneliness score</td>
<td></td>
<td>1.06</td>
<td>0.99–1.14</td>
<td>0.09</td>
</tr>
<tr>
<td>Model 2: model 1 +</td>
<td>19.3</td>
<td></td>
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<td>0.04</td>
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<tr>
<td>Age</td>
<td></td>
<td>1.05</td>
<td>1.02–1.09</td>
<td>&lt;0.01</td>
</tr>
<tr>
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<td>0.30–0.96</td>
<td>0.04</td>
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<tr>
<td>Model 3: model 2 +</td>
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<td></td>
<td>0.05</td>
</tr>
<tr>
<td>AUCg</td>
<td></td>
<td>0.40</td>
<td>0.10–1.61</td>
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</tr>
<tr>
<td>AUCl</td>
<td></td>
<td>0.91</td>
<td>0.53–1.56</td>
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<tr>
<td><strong>Network size</strong></td>
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<td></td>
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<tr>
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<tr>
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<td>0.01</td>
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<tr>
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<tr>
<td>AUCg</td>
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<tr>
<td>AUCl</td>
<td></td>
<td>0.86</td>
<td>0.50–1.46</td>
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</table>

AUCg, area under the curve with respect to the ground; AUCl, area under the curve with respect to the increase.

and partner status. There were no significant associations between cortisol measures and mortality. There were no significant interactions with depression status, sex or partner status. The sensitivity analyses in the depressed group showed largely the same results: no significant associations between loneliness and mortality \(\left(\chi^2 = 0.58, \text{HR} 1.03, 95\% \text{ CI} 0.95–1.13\right)\) or between social network size and mortality \(\left(\chi^2 = 0.003, \text{HR} 0.99, 95\% \text{ CI} 0.67–1.46\right)\). However, age and partner status were no longer significantly associated with mortality in the depressed group.

Loneliness as a dichotomous variable was not a significant predictor of mortality either \(\left(\chi^2 = 0.27, \text{p value} 0.60\right)\). The same was true for social network size as a dichotomous variable \(\left(\chi^2 = 1.24, \text{p value} 0.26\right)\). There were no significant interactions with sex, depression or partner status.

Since no significant associations were found between social network size and cortisol, between social network size and mortality, between loneliness and mortality, nor between mortality and cortisol measures, we did not execute mediation analyses.

**Discussion**

This study aimed to investigate the associations between social network size and cortisol, as well as between social network size and mortality and between loneliness and mortality, in a sample of 443 older adults aged 60–93 years. There were no significant associations between social network size and CAR, morning cortisol, dexamethasone suppression or diurnal slope. In other words, participants with larger networks did not differ from participants with smaller networks with respect to cortisol values. Nonetheless, they did differ on other variables, such as depression status, number of somatic diseases and loneliness scores. Interaction between cortisol factors and depression was not significant, however. This is in line with a study analyzing the associations between cortisol factors and depression in older adults (Rhebergen et al., 2015). In this study depression severity was not associated with cortisol values. Our results are not in line with the study by Grant et al. (2009) that showed a significant association between social isolation and higher CAR. However, in their study, the mean age was 52 years, and thus the results are not comparable to the present study, in which the mean age is 70 years. Also, the social isolation variable was not social network size but rather frequency of contact. Other studies are more in line with our results. For example, the study by Stafford et al. (2013), who investigated different measures of social isolation in a cohort of older adults aged 60–64 years, showed that social network size was not associated with cortisol measures, but that living alone and not being married were associated with greater cortisol output and higher CAR. However, living alone and not being married are different measures from social network size. Turner-Cobb, Sephton, Koopman, Blake-Mortimer, and Spiegel (2000) investigated the associations of social network size and social support with cortisol measures in a group of female cancer patients with a mean age of 53 years and concluded that there was no association between network size and cortisol measures. Lai et al. (2012) did not find a significant association between social network size and cortisol measures in a group of Chinese men and women aged 59–86 years. A post-hoc analysis in our study showed that partner status was significantly associated with lnAUCg \(\left(B = -0.10; \text{p value} 0.046\right)\), indicating that like in the study by Stafford et al. (2013), there was an association between having a partner and cortisol output, with having a partner being associated with 0.90 lnAUCg compared to not having a partner. In other words:
not having a partner was associated with higher cortisol output.

The lack of significant results in the analyses of the associations between loneliness and social network size at baseline and mortality six years later leads to the conclusion that loneliness and social network size are not associated with mortality in our group of participants. Partner status, together with age, was a much more important predictor. These results contradict other studies that found significant associations between mortality and either social network size (de Brito et al., 2017; Ellwardt et al., 2015; Giles, Glonek, Luszcz, & Andrews, 2005; McLaughlin et al., 2011; Shye, Mulloloy, Freeborn, & Pope, 1995; Vogt, Mulloloy, Ernst, Pope, & Hollis, 1992) or loneliness (Drangeset, Eide, Kirkevold, & Ranhoff, 2013; Elovainio et al., 2012; Perissinotto et al., 2012; Tilvis, Laitala, Routasalo, & Pitkälä, 2011). In two of these studies, the number of participants was comparable to ours (Shye et al., 1995, p. 455; Vogt et al., 1992, p. 451), but since the length of follow-up was much longer (15 years), the number of deaths was considerably higher. This might partly explain the difference in outcome.

Our results are in line with several other studies on the associations between mortality and loneliness (Ellwardt et al., 2015; Holwerda et al., 2016; lecovich, Jacobs, & Stessman, 2011; Julsing, Kromhout, Geleijnse, & Giltay, 2016; Jylha & Aro, 1989; Luo & Waite, 2014; Olaya et al., 2017; Olsen et al., 1991; Steptoe et al., 2013; Stessman, Rottenberg, Shimshiklashvilli, Ein-Mor, & Jacobs, 2014; Sugisawa, Liang, & Liu, 1994; Tabue Teguo et al., 2016; Tanskanen & Anttila, 2016) and social network size (Cerhan & Wallace, 1997) in older adults. In most of these studies the number of participants was larger (from 600 up to 14,000), with a length of follow-up varying from 3 to 22 years. Typically, in most studies significance was lost in the multivariable analyses with somatic diseases and/or depression as covariates. Contrarily, in our study even the univariable associations were not significant. Because we did find associations with partner status and age, the relatively small number of deaths in the present study is not a satisfying explanation. Our sample differs from most of the population-based mortality studies in older adults because of the large number of depressed participants. The sensitivity analyses showed that in the group with only depressed participants, age and partner status were no longer significantly associated with mortality. Because depression has been found to be related to a higher risk of cardiovascular and all-cause mortality in different age groups (Li et al., 2020; Saz & Dewey, 2001; Wei et al., 2019), this could mean that depression is more strongly correlated with mortality than either age or partner status.

We chose network size as an objective indicator of social isolation. It might be that network size is not the most relevant social isolation variable in the association with mortality. A study by Ali, Nilsson, Weuve, Rajan, and Mendes de Leon (2018) concluded that network diversity might be more important than network size with respect to the impact on mortality. Another possible explanation for the lack of significant associations with mortality is the notion that as people get older, the factors that play a role in mortality risk become more diverse. This is illustrated by the conclusions in the meta-analysis by Holt-Lunstad, Smith, Baker, Harris, and Stephenson (2015) that the effects of loneliness and social isolation on mortality diminish with age as well as with the addition of more covariates (Holt-Lunstad et al., 2015). Possibly, the same applies to the factors that play a role in cortisol levels. With aging, the amplitude of the cortisol rhythm has been described to diminish (Belvederi Murri et al., 2014; Liyanarachchi, Ross, & Debono, 2017). Consequently, variations in this already diminished rhythm can be harder to demonstrate. In addition, the HPA-axis in older age is more vulnerable for dysregulation by central nervous system diseases, which are more prevalent in older adults (Belvederi Murri et al., 2014). Also more prevalent are physical diseases. It has been demonstrated that physical diseases are associated with increased cortisol levels (Belvederi Murri et al., 2014).

In the present study, age and partner status were the most important predictors of mortality. This is in line with other studies that concluded marital status was significantly associated with mortality (Cerhan & Wallace, 1997; lecovich et al., 2011; Saito et al., 2020; Stessman et al., 2014). A recent study by Manvelian and Sbarra (2020) showed that having fewer than 4–6 close relationships was associated with higher mortality in older adults that lost their partner. However, in our study we investigated the reverse situation and did not find a significant interaction between social network size and partner status, meaning that having a partner is not protective in the association between network size and mortality. Neither did we find a significant interaction between loneliness and partner status. However, a study by O’Suilleabhaín et al. (2019) showed that in older adults living alone, emotional loneliness was associated with increased mortality risk. They concluded that the loss of an intimate relation could be the harmful ingredient that causes the higher mortality risk. Other authors emphasize the difference between men and women with regard to the effect of marital status on mortality risk (Bulanda, Brown, & Yamashita, 2016). Whereas for men marital status is associated with mortality risk regardless of the quality of the marriage, for women the marital quality is more important. However, we found no differences between men and women. Whether different aspects of social relationships are important for men versus women in their effects on mortality is an interesting subject for further study.

The strengths of this study are the fact that we could analyze both subjective (loneliness) and objective (network size) aspects of social relationships; the opportunity to combine them with cortisol measures and survival data; the inclusion of both depressed and non-depressed participants; and the availability of several relevant covariates.

However, this study also has some limitations. The follow-up time was 6 years, which may have been too short for a study investigating associations with mortality; the cortisol study was a cross-sectional study, which in case of significant associations prohibits making causal inferences; as already mentioned, it might be that social network size is not the most relevant objective indicator of social relationships; we did not include other aspects of social network, such as social support; finally, the sample size was rather small for a mortality study.

In conclusion, there was no significant association between social network size and cortisol. Neither did we
find significant associations between loneliness and social network size and mortality. The most important predictors of mortality proved to be partner status and age, although this was different for depressed compared with non-depressed participants. Since loneliness and social network can influence depression severity (van Den Brink et al., 2018), it is possible that prevention aimed at diminishing loneliness and expanding the social network indirectly has a favorable influence on mortality. It should be stressed that as people grow older the variety of factors that influence mortality risk increases, thus diminishing the effect of a single factor. This implicates that prevention of early morbidity and mortality in older adults is not simply a matter of aiming at one particular factor but that it should be tailored to specific needs and risks. Discovering which risks are more prevalent in certain subgroups of older adults remains an interesting subject for further study.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**References**


