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BRIEF REPORT

Depression and loneliness may have a direct connection without mediating factors

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ABSTRACT

Purpose of the article: There is growing interest in loneliness and its various adverse effects on mental and physical health. While depression is one of the adverse health effects associated with loneliness, there have been some limitations in previous studies: 1) Research has mostly been carried out either in depressed patient samples or in general population samples with depressive symptoms as an outcome, 2) the follow-up times have been rather short, and 3) the mechanisms through which loneliness associates with depression are still unclear.

Materials and methods: We examined the association between loneliness and incident depression and possible mechanisms underlying this association in a population-based sample of middle-aged men ($N = 2339$; mean age 53; mean follow-up time 23.5 years). The association between loneliness and depression was explored with Cox proportional hazard analysis, and mediation analyses were performed with the PROCESS macro for SPSS. We used 13 health and lifestyle-related variables as covariates for adjustments in multivariate models and as mediators in simple mediation models.

Results: Those with depression as an outcome ($n = 99$) had significantly higher loneliness scale scores at baseline, and baseline loneliness was associated with depression, despite adjustments for potential confounding factors. No mediating factors were observed.

Conclusions: There was a strong direct association between loneliness and the incidence of depression. Based on our results, we encourage future researchers to look for possible mediators in wider range of variables.

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Loneliness; depression; prospective study

Introduction

Loneliness has been described as dissatisfaction with the discrepancy between desired and actual social relationships [1,2]. According to previous studies, loneliness is associated with negative health behavior [3], various health problems and physiological changes [4], and a lower socioeconomic status [5]. A connection between loneliness and depression was already suggested in the 1980s [6]. However, to date, most studies on the relationship between depression and loneliness have been cross-sectional and have used depressive symptoms as an outcome variable. Longitudinal studies in general populations have mostly used symptoms, while diagnosis studies have usually involved samples of depressed patients. So far, few studies (see Chicago Health, Aging and Social Relations Study [7], The Irish Longitudinal Study on Ageing (TILDA) [8], NEIL Memory Research Unit [9]) have focused prospectively on the connection between loneliness and depression in a general population while using depression diagnosis as an outcome. In these studies, the follow-up time has been rather short, ranging from two to six years. In conclusion, despite a wide range of studies concerning the association between depression and loneliness, there is lack of longitudinal studies in general populations with depression diagnosis as an outcome.

Recently, the first umbrella review providing a qualitative evidence synthesis of the risk factors and health outcomes associated with loneliness was published [10]. Two studies that were included in the umbrella review had depression or depressive symptoms as an outcome. One of these was a meta-analysis containing cross-sectional studies, while the other was a systematic review analyzing longitudinal quantitative studies conducted in clinical samples. They found that greater loneliness predicts a poorer outcome in terms of the severity and remission of depression [10]. Furthermore, since loneliness has been shown to correlate with adverse health choices [11,12], which in turn are connected to depression,

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Solmi et al. [10] suggested that there may be factors mediating or moderating the connection. Therefore, we aimed to examine the effects of loneliness on incident depression in a longitudinal general population sample with the advantage of several possible confounding factors. To further investigate the mechanisms underlying the connection between loneliness and depression, we conducted mediation analyses with all the available covariates.

Materials and methods

The Kuopio Ischemic Heart Disease (KIHD) Study, approved by the Research Ethics Committee of the University of Kuopio, is an ongoing study designed to investigate the risk factors and outcomes of chronic diseases. The study sample was recruited in two cohorts: the first cohort enrolled between 1984 and 1986, and the second cohort enrolled between 1986 and 1989. The sample comprised a total 2682 men (82.9% of those eligible) with a mean age of 53 (SD 5.2) years at baseline. The dataset had 3.8% of values missing. The missing data were observed to be missing completely at random (Little's MCAR test chi-square $= 0$, $p = 1$) and were imputed with the expectation-maximization method.

To avoid reversed causality, those with elevated depressive symptoms at baseline (Human Population Laboratory (HPL) depression scale scores ≥ 5) were excluded [13], leaving 2339 men to be followed up for a mean of 23.5 (SD 8.9) years. In our analyses, to avoid multicollinearity, we used a modified version of the HPL depression scale without two loneliness-related questions. Data on depression (diagnosed according to the International Classification of Diseases, ICD) were obtained using computer linkage to the national hospital discharge and outpatient registers at the end of 2017.

The Loneliness Scale consists of 11 items that measure the discrepancy between actual and desired social contacts [1], subjective satisfaction with one's social life, and feelings of loneliness. Cronbach's alpha for the loneliness scale was 0.730 [14].

Subjects were defined as smokers if they reported having ever smoked on a regular basis [15]. Alcohol consumption was assessed by using a structured quantity–frequency method with a drinking behavior questionnaire covering the previous 12 months [16]. The energy expenditure resulting from conditioning leisure time physical activities was assessed using a modified version of the Minnesota Leisure Time Physical Activity Questionnaire [17]. The socioeconomic status score consists of information about occupation, income, housing tenure, and ownership of material goods [18]. For the medical examination, participants were requested to fast overnight, abstain from smoking for 12 h, and avoid alcohol use for three days before obtaining blood samples. Due to increased C-reactive protein (CRP) levels observed in earlier studies [19], we used high-sensitivity CRP (hs-CRP) as a measure of low-grade inflammation. Hs-CRP was measured with an immunometric assay, the Immulite high-sensitivity CRP assay (Diagnostic Products Corporation, Los Angeles, California, USA), which has been standardized against the World Health Organization (WHO) international reference standard for CRP immunoassay, standard 85/506. Systolic blood pressure was measured using a random-zero mercury sphygmomanometer. Low-density lipoprotein (LDL) portions were extracted from fresh serum by a method combining ultracentrifugation and precipitation during the medical examination [20]. Body mass index (BMI) was recorded as the weight in kilograms divided by the square of the height in meters. A history of cardiovascular disease (CVD) was defined as having a diagnosis of CVD other than high blood pressure. An estimate of the average number of hours slept at night was obtained using self-administered questionnaires [21]. Slightly modified Baltic Sea Diet Scores (BSDS) were calculated based on four-day food records collected at baseline [22].

Group differences in the categorical variables were analyzed with the chi-squared test, while the Student's *t*-test was used in comparisons of normally distributed variables and the non-parametric Mann–Whitney *U* test in comparisons of other continuous variables.

Cox proportional hazards analysis (method: Enter) was used to examine the association between loneliness and depression. The variables for adjustments were chosen based on their possible connection with either loneliness or depression. Altogether, nine models were constructed (Table 2): the basic model (Model 1) was adjusted for age and year of examination; in the SES model (Model 2) [5], SES scores were added to Model 1 to investigate the possible confounding effect of socioeconomic status. In the lifestyle model (Model 3), alcohol consumption [23], smoking [24], and physical activity [11] were added to Model 1 to investigate the possible confounding effects of lifestyle factors. In the diet model (Model 4) [11], BSDS was added to Model 1 to control for effects that diet may have on depression. In the sleep model (Model 5) [25], self-reported sleep quantity was added to Model 1 to investigate the possible confounding effect of sleep. In the depression model (Model 6), HPL depression score residuals from the baseline were added to Model 1 to investigate the effect that baseline depressive symptoms have on incident depression. In the inflammation model (Model 7) [26], hs-CRP levels were added to Model 1 to investigate the possible confounding effects of low-grade inflammation. In the physiological changes model (Model 8) [27,28], Model 1 was further adjusted for systolic blood pressure, LDL-cholesterol, BMI, and CVD history. In Model 9, all previous confounders were inserted in the model at the same time. The proportional hazard assumption was checked by plotting residuals against the follow-up time. These residuals were randomly distributed without any trends. Simple mediation analysis was performed with the conditional modeling program PROCESS macro v.3.4.1 for SPSS [29]. All analyses were conducted using IBM SPSS (version 26) statistical software.

Results

Those with depression as an outcome ($n = 99$) had significantly higher loneliness scale scores at baseline and higher

Table 1. Background characteristics of participants who were diagnosed with depression during the follow-up and those who were not.

	Depression ($n = 99$)	No depression ($n = 2240$)	Test value	p
Loneliness	15 (8.25–19.99)	12 (8–17)	−2.74	0.006[c]
HPL depression	1 (0–3)	1 (0–2)	−3.03	0.002[c]
Age, years, mean (SD)	52.09 (5.43)	53.02 (5.16)	2.474	0.078[b]
SES, mean (SD)	12.66 (5.0)	12.08 (5.13)	0.199	0.274[b]
Smoking, *n* (%)	34 (34.3)	698 (31.2)	0.447	0.504[a]
Alcohol, g/week	30.5 (6.1–115)	42.8 (6.5–115)	−1.04	0.298[c]
Baltic Sea Diet Score, mean (SD)	12.56 (3.61)	12.91 (3.99)	1.355	0.390[b]
Sleeping quantity, mean (SD)	2.88 (1.62)	2.93 (1.63)	0.040	0.751[b]
Physical activity, kcal/d	86 (33–182)	88 (31–193)	−0.375	0.707[c]
BMI, mean (SD)	27.07 (3.31)	26.82 (3.5)	0.923	0.483[b]
Systolic blood pressure, mean (SD)	134.09 (15.79)	132.09 (15.79)	0.376	0.222[b]
LDL-C mmol/l, mean (SD)	3.95 (0.92)	4.06 (1.02)	0.982	0.291[b]
Hs-CRP mg/l	1.08 (0.55–1.99)	1.3 (0.73–2.48)	−1.745	0.081[c]
CVD history, *n* (%)	29 (29.3)	792 (33.9)	1.531	0.216[a]

Note: Values are medians (interquartile ranges), unless otherwise stated. SD: standard deviation; HPL: Human Population Laboratory; SES: socioeconomic status; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; CVD: cardiovascular disease.
[a]Chi-squared test.
[b]Student's *t*-test.
[c]Mann–Whitney *U* test.

Table 2. Hazard ratios of loneliness (*z*-score) for incident depression during the follow-up.

Model, covariates	Hazard ratio (CI 95 %) *p*-value
Model 1 – Age, Year of examination	1.042 (1.022–1.063), $p < 0.001$
Model 2 – Age, Year of examination, SES	1.041 (1.021–1.062), $p < 0.001$
Model 3 – Age, Year of examination, Lifestyle (alcohol consumption, smoking, physical activity)	1.042 (1.022–1.063), $p < 0.001$
Model 4 – Age, Year of examination, Baltic Sea Diet Score	1.041 (1.021–1.062), $p < 0.001$
Model 5 – Age, Year of examination, Sleep quantity	1.042 (1.022–1.063), $p < 0.001$
Model 6 – Age, Year of examination, HPL depression scale score residuals	1.032 (1.010–1.055), $p = 0.005$
Model 7 – Age, Year of examination, hs-CRP	1.042 (1.022–1.063), $p < 0.001$
Model 8 – Age, Year of examination, Physiological changes (Mean systolic blood pressure, LDL-cholesterol, BMI, CVD history)	1.042 (1.022–1.063), $p < 0.001$
Model 9 – All the variables from models 1–8	1.033 (1.010–1.056), $p = 0.005$

Note: Hazard ratios show the increase in the risk of incident depression for each 1-SD increase in the Loneliness Scale score.
Abbreviations: SES: socioeconomic status; HPL: Human Population Laboratory; hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index; LDL: low-density lipoprotein; CVD: cardiovascular disease.

HPL depression scale scores. There were no other baseline differences between groups (Table 1).

In multivariate models (Table 2), loneliness associated with depression despite adjustments for all confounders. When adjusted for HPL depression scale score residuals, or with all covariates in the same model, the HR decreased by approximately 1% and the p-value increased from <0.001 to 0.005. In simple mediation analyses, only HPL depression scale score residuals mediated the effect of loneliness on incident depression (indirect effect $ab = 0.01$, bootstrapped 95% CI 0.01–0.02). None of the other continuous variables included in Cox proportional hazard models mediated the effect of loneliness on incident depression [age: $ab = -0.001$ (–0.002–0.001); SES: $ab = 0.001$ (–0.001–0.001); alcohol $ab = 0.002$ (–0.001–0.001); physical activity $ab = 0.0003$ (–0.001–0.001); diet $ab = 0.003$ (–0.002–0.004); sleep $ab = 0.0001$ (–0.002–0.002); hs-CRP $ab = -0.0004$ (–0.003–0.001); BP $ab = 0.0004$ (–0.001–0.002); LDL-C $ab = -0.001$ (–0.003–0.0004); BMI $ab < 0.001$ (–0.001–0.001)]. Instead, loneliness had a direct effect on incident depression.

Discussion

In our sample, 99 patients (4.2%) were diagnosed with depression during the follow-up, even after we excluded those with increased HPL depression scores at baseline. Our results indicate that loneliness has an association with incidence depression in a longitudinal setting, despite adjustments for several possible confounding factors. No mediating factors were identified and the effect of loneliness on depression was direct.

In the 1980s, it was believed that loneliness is merely an aspect of depression. Later loneliness, was seen more as an independent risk factor for depression [6]. Recently, a bidirectional connection between loneliness and depression has been suggested: lonely individuals are more likely to develop maladaptive behaviors, which will in turn increase the feeling of loneliness [30]. Loneliness was found to mediate the effect of living alone on depression in a cross-sectional study [31], while in a 2-year follow-up study, loneliness was predicted by, but did not predict, depressive symptoms [9]. Looking for the mechanism or the pathway through which loneliness and depression are interconnected is the next step of research in this field. Despite detecting a strong longitudinal association between loneliness and incident depression, we observed no mediators among lifestyle or health-related variables. Instead, according to the literature, the mediators may be more psychological, such as resilience [32] or self-disgust [33].

Strengths and limitations

The main strength of our analysis is the availability of various covariates to be tested as possible mediators for the relationship between loneliness and depression. Furthermore, we

were able to use both loneliness and depression as continuous variables, thus avoiding loss of information. The main weakness of our study is that the sample consisted of middle-aged Finnish men, and the results cannot therefore be generalized to other populations.

Conclusions

There was a strong direct association between loneliness and the incidence of depression, which remained significant despite adjustments for any confounding factors. We did not find mediators among lifestyle and health-related variables. Based on our results, we encourage future researchers to look for possible mediators in wider range of variables.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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SLK and TT led the conception and design of the analyses; SLK conducted the analyses and wrote the first draft of the manuscript. TT, NJ, SML, AR, SH reviewed and edited the manuscript. JK provided administrative support. All authors approved the final version of the submitted manuscript.

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