

Cardiovascular and all-cause mortality attributable to loneliness in older Swedish men and women

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Abstract

Background. This study examined whether loneliness predicts cardiovascular- and all-cause mortality in older men and women.

Methods. Baseline data from the Gothenburg H70 Birth Cohort Studies, collected during 2000 on 70-year-olds born 1930 and living in Gothenburg were used for analysis ($n=524$). Mortality data was analyzed until 2012 through Swedish national registers.

Results. Perceived loneliness was reported by 17.1% of the men and 30.9% of the women in a face-to-face interview with mental health professional. A total of 142 participants died during the 12-year follow-up period, with 5 334 person-years at risk, corresponding to 26.6 deaths/1000 person-years. Cardiovascular disease accounted for 59.2% of all deaths. The cumulative rates/1000 person-years for cardiovascular mortality were 20.8 (men) and 11.5 (women), and for all-cause mortality 33.8 (men) and 20.5 (women), respectively. In Cox regression models, no significant increased risk of mortality was seen for men with loneliness compared to men without loneliness (cardiovascular mortality HR 1.52, 95% CI 0.78 - 2.96; all-cause HR 1.32, 95% CI 0.77 - 2.28). Increased risk of cardiovascular mortality was observed in women with loneliness compared to those without (HR 2.25 95% CI 1.14 - 4.45), and the risk remained significant in a multivariable-adjusted model (HR 2.42 95% CI 1.04 - 5.65).

Conclusions. Loneliness was shown to be an independent predictor of cardiovascular mortality in women. We found no evidence to indicate that loneliness was associated with an increased risk of either cardiovascular- or all-cause mortality in men.

Introduction

Loneliness is a subjective, negative emotional state, generally defined as perceiving less social contacts than desired [1]. Loneliness may be experienced by people of all ages, however, with advancing age, social contacts are reduced due to factors, such as losses of spouse or friends or mobility impairments, resulting in a higher prevalence of loneliness in elderly populations [2]. A large body of evidence suggests that loneliness is a major risk factor for poor mental and physical health in later life [3]. For instance, feeling of loneliness is reported to be associated with increased risks of cardiovascular diseases (CVD), depressive symptoms, impaired cognitive performance, and dementia [3]. Although there is considerable literature on the impact of loneliness on morbidity, there is modest data on its effect on mortality [3]. These studies have reported higher rates of mortality among individuals with loneliness [4-11]. However, findings across these studies are inconsistent on whether loneliness independently predicts mortality risk after adjusting for initial health and social factors. The aim of the present study was to examine whether loneliness independently predicts cardiovascular- and all-cause mortality in older people after adjusting for initial health status, health behaviors, depression, living alone and economic situation.

Methods

Study population

The Gothenburg H70 Birth Cohort Studies (the H70 studies) are ongoing population-based longitudinal studies of health and ageing. Full details of these studies have been reported elsewhere [12-16]. In brief, initiated in 1971, the H70 studies are a series of cohort studies of older men and women living in Gothenburg, Sweden. Seventy-year-old men and women listed in national population registers in Gothenburg were systematically selected based on their birth dates and they underwent extensive medical, social, psychiatric, and physical examinations.

For the purpose of the present study, baseline data on the 1930 birth cohort collected during 2000 was used (n = 524, response rate 70%). Forty-seven percent of non-participants was surveyed for a shorter health interview. Participants and non-participants were similar regarding self-rated health, history of myocardial infarction, diabetes or smoking status, but married men were significantly overrepresented among participating men [17].

All participants gave informed consent to participate in the study. The study complied with the Declaration of Helsinki principles, and was approved by the Regional Ethics Committee for Medical Research at the University of Gothenburg.

Assessment of loneliness

Self-perceived feeling of loneliness was assessed by a single question as 'do you feel lonely?' There were four alternative responses where 1 indicated never feeling lonely, 2 seldom, 3 sometimes, and 4 very often (see **Table 1** for sample distribution). The four categories were then merged into a dichotomous variable as 0 = not lonely (responses 1-2), and 1 = lonely (responses 3-4).

Table 1. Number and percentages of men and women in each of the four response categories of self-perceived feelings of loneliness.

	All	Never	Seldom	Sometimes	Often
		(response 1)	(response 2)	(response 3)	(response 4)
	N	n (%)	n (%)	n (%)	n (%)
Men	240	147 (61.3)	52 (21.7)	39 (16.3)	2 (0.8)
Women	272	104 (38.2)	84 (30.9)	70 (25.7)	14 (5.1)
All	512	251 (49.0)	136 (26.6)	109 (21.3)	16 (3.1)

Mortality

Based on unique personal identification numbers and using the Swedish national registers (the national population register and the national cause of death register), cohorts were followed for 12 years from the date of their baseline examination or until death. Cardiovascular deaths were those with International Classification of Diseases, 10th Revision (ICD-10) codes I.00-I.99.

Other covariates

Adverse socioeconomic status, health and health related behavioral factors that have previously been shown to be associated with loneliness [18-20] were included as possible confounding factors. Current perceived economic situation was assessed using a seven-point scale ranging from excellent to very bad (coded from 1 to 7). The seven-point scale was then merged into three categories: good (scale points 1-3, excellent, very good, good), Average (scale point 4), and poor (scale points 5-7, not very good, bad, very bad). Living alone was categorized as individuals who are single, or divorced, or widowed and live alone versus individuals who live with a partner (married/cohabiting/having partner but lives separate or live-apart-together or occasionally live together, Swedish term is '*särbo*') or with someone else. Smoking status was categorized as current smoker (regular or occasional), previous smoker, and never smoker. Leisure time physical activity was defined as moderate/regular versus inactive. Alcohol consumption was measured with questions regarding weekly consumption of beer, wine, and spirits in centiliters (cl) during the past month. Based on these volumes, average weekly grams of alcohol consumption were calculated using conversion factors based on average alcohol concentration by volume (spirits 1 cl = 3 g, wine 1 cl = 1 g, beer >3.5% 1 cl = 1/3 g). Body mass index (BMI) was calculated from measured weight and height (weight in kg/height in m²). Previous history of having (yes/no) cancer, diabetes, coronary heart disease and stroke was based on self-report as well as from medical examinations conducted by a study physician. Systolic and diastolic blood pressure (SBP, DBP) were measured in the sitting position after a minimum of 5 min of rest. Blood samples were drawn from an antecubital vein and serum triglyceride measurement was determined according to standard laboratory procedures. Impaired mobility was defined based on a six-item scale of activities of daily living (ADL). The ADL scale measured self-reported difficulties in performing daily life activities including transferring, dressing, bathing, using toilet, eating, and continence. Each item was coded as 0 = no need of help from another person, and 1 = need help. A composite index was created by summing up all the six items ranging from 0 to 6 (need no help to need help in all six activities). The index was then dichotomized as 0 (no impaired mobility) and 1 (impaired mobility, scale 1-6). Based on symptoms elucidated during a psychiatric examination, major depression was diagnosed according to the DSM-5 criteria (American Psychiatric Association) [21], and minor depression according to the DSM-IV research criteria [22]. Definition of these variables has been described previously [23].

Statistical analysis

Using descriptive statistics, differences in the distribution of baseline characteristics in men and women according to their loneliness status were examined using the Pearson χ^2 -test for categorical variables and Student's t-test for continuous variables. Descriptive statistics are presented as percentages or mean values with standard deviations (SD). All P-values are two-sided and values of < 0.05 were considered statistically significant. The survival function for the 12-year period according to loneliness status was assessed using the Kaplan Meier method, and the log-rank test was used to evaluate group differences. Cox proportional hazard regression models were used to study the association between loneliness status at baseline and cardiovascular and all-cause- mortality during 12-year follow-up. Both unadjusted and

multivariable adjusted regressions were carried out separately for cardiovascular- and all-cause mortality. Factors that were shown to be associated with loneliness were included in multivariable models. Estimates derived from Cox regressions are presented in graphical format showing hazard ratios (HR) and 95% CI. Statistical analyses were performed using SPSS, Windows version 25.0 (SPSS Inc., Chicago, IL, USA) and graphics were produced using R version 3.4.3 (The R Foundation for Statistical Computing).

Results

The current analyses were conducted on 512 participants (240 men, 272 women) after exclusion of 12 individuals with missing data on loneliness. A total of 125 (24.4%) participants reported being lonely at baseline. The prevalence of loneliness was 17.1% (n = 41) in men and 30.9% (n = 84) in women ($p = 0.000$).

Loneliness and background characteristics:

Table 2 presents background characteristics of men and women according to their loneliness status. Men with loneliness reported more often poor economy, living alone, and physical inactivity and were more often diagnosed with depression than men with no loneliness. No significant differences were observed regarding smoking, alcohol consumption, BMI, and history of any health related variables. Women with loneliness more often reported poor economy, chronic bronchitis, and living alone, and were more often diagnosed with depression than women without loneliness. No significant differences were observed regarding smoking, physical activity, alcohol consumption, BMI, or history of other health related variables.

Table 2. Distribution of baseline characteristics among men and women according to their perceived loneliness status (N = 512).

	Men			Women		
	N = 240		<i>p</i> -value	N = 272		<i>p</i> -value
	Lonely N = 41	Not lonely N = 199		Lonely N = 84	Not lonely N = 188	
Current perceived economic situation						
Good	47.5 (19)	77.7 (150)		48.8 (39)	72.2 (132)	
Average	27.5 (11)	15.6 (30)		38.8 (31)	17.8 (32)	
Poor	25.0 (10)	6.7 (13)	0.000	12.5 (10)	10.0(18)	0.001
Living alone	52.5 (21)	9.1 (18)	0.000	60.8 (48)	39.2 (71)	0.001
Smoking status:						
Never smoker	22.0 (9)	33.3 (66)		51.2 (42)	62.5 (115)	
Previous smoker	53.6 (22)	53.5 (106)		25.6 (21)	23.9 (44)	
Current smoker	24.4 (10)	13.2 (26)	0.119	23.2 (19)	13.6 (25)	0.109
Physical activity:						
Regular	38.5 (15)	64.4 (125)		32.5 (25)	35.8 (63)	
Inactive	61.5 (24)	35.6 (69)	0.003	67.5 (52)	64.2 (113)	0.609
BMI	27.13 ± 3.49	26.88 ± 3.95	0.704	26.63 ± 4.04	27.22 ± 4.69	0.330
Alcohol (gm/per week)	51.18±64.61	76.29±108.27	0.071	25.69±31.14	34.03±52.14	0.228
Health related variables:						
SBP (mm Hg)	151.97±22.46	157.71±20.40	0.146	151.43±23.85	153.70±22.07	0.504
DBP (mm Hg)	84.76±8.94	87.81±9.95	0.103	85.40±11.85	84.36±10.47	0.517
Triglyceride (mmol/l)	1.30±0.54	1.39±0.57	0.386	1.40±0.56	1.41±0.85	0.995
Diabetes	12.2 (5)	11.2 (22)	0.850	11.5 (9)	9.0 (16)	0.536
CHD	17.1 (7)	10.7 (21)	0.246	5.0 (4)	5.5 (10)	0.877
Stroke	2.4 (1)	5.1 (10)	—	9.8 (8)	7.0 (13)	0.445
Cancer	12.2 (5)	15.3 (30)	0.610	18.2 (14)	12.6 (22)	0.248
Chronic bronchitis	19.5 (8)	13.2 (26)	0.293	25.6 (20)	15.2 (27)	0.046
Arthritis	17.1 (7)	17.3 (34)	0.966	34.6 (27)	31.8 (56)	0.661
Impaired mobility	17.9 (7)	9.2 (17)	0.108	14.9 (11)	10.6(18)	0.343
Depression:						
No	68.4 (26)	95.7 (180)		61.3 (49)	92.8 (168)	
Minor	21.1 (8)	4.3 (8)		25.0 (20)	5.5 (10)	
Major	10.5 (4)	0	0.000	13.8 (11)	1.7 (3)	0.000

Values presented in this table are mean±SD or percentage with number of subjects in parenthesis. BMI = body mass index (wt in kg/ht in m²), SBP = systolic blood pressure, DBP = diastolic blood pressure, CHD = coronary heart disease.

Gender, loneliness and mortality:

A total of 142 (27.7%) participants died during the 12-year follow-up period, with a median follow-up of 11 years and 5 334 person-years at risk, corresponding to 26.6 deaths per 1000 person-years. Cardiovascular disease accounted for 59.2% (n = 84) of all deaths, which corresponds to 15.8 deaths per 1000 person-years. The cumulative rates per 1000 person-years for cardiovascular mortality were 20.8 (men) and 11.5 (women), and for all-cause mortality were 33.8 (men) and 20.5 (women), respectively.

Kaplan Meier analysis showed no significant difference in survival between men with and without loneliness for either cardiovascular- or all-cause mortality (log rank, $p > 0.05$) (**Figures 1 a and 1 b**). For women, Kaplan Meier curves showed no difference in all-cause mortality by loneliness status (**Figure 1 c**), but a lower survival rate was observed among women with loneliness compared to women with no loneliness regarding cardiovascular mortality (log rank, $p = 0.017$) (**Figure 1 d**).

Figure 2 presents HRs and 95% CI of (a) cardiovascular and (b) all-cause mortality according to gender and loneliness status. Similar to Kaplan Meier results, no significant increased risk of mortality was observed for men with loneliness compared to men with no loneliness for both cardiovascular (HR 1.52 95% CI 0.78-2.96) and all-cause mortality (HR 1.32 95% CI 0.77-2.28). In all-cause mortality, no significant increased risk of mortality was seen for women with loneliness compared to women with no loneliness (HR 1.64 95% CI 0.98-2.76). However, women with loneliness had significantly higher risks of cardiovascular mortality compared to women with no loneliness (HR 2.25 95% CI 1.14 - 4.45). The high risks of cardiovascular mortality in women remained significant in the multivariable-adjusted model (2.42 95% CI 1.04 - 5.65).

Discussion

This study examined if loneliness at age 70 was prospectively associated with cardiovascular- and all-cause mortality over a 12-year follow-up period, after controlling for initial health status, health behaviors, depression, and other social factors. We found that loneliness was an independent predictor of cardiovascular mortality in women, while there was no association with all-cause mortality. Among men, we found no evidence of an association between loneliness and subsequent death whether cardiovascular- or all-cause both in unadjusted or multivariable-adjusted models.

The strengths of the study included the population-based samples of both men and women and the comprehensive examinations data on socio-demographic factors, medical history, and clinical- and physical measurements, including loneliness status. However, this study also had a number of limitations. First, although the response rate at baseline was 70%, which is higher than in many other studies [24], we cannot exclude the possibility that participants were healthier than non-participants. Although a short health survey in non-participants revealed that participants and non-participants were similar in terms of health history and health related behaviors, married men were overrepresented among participating men [17]. This may imply that lonely men are underrepresented in the sample, as unmarried status is strongly associated with loneliness [19], which may have caused selection bias in our study. Another limitation was the definition of loneliness, which was assessed with a single-item question. This may result in underreporting due to the stigma associated with being identified as lonely [2, 25]. Therefore, this single measurement may not capture the overall influence of loneliness on mortality. This single item question of loneliness, however, is most common and a widely used measure [3], which previously has been shown to predict mortality [5, 7, 9].

As expected, feeling lonely was more common in women than in men. A recent review concluded that women are more likely to report loneliness than their male counterparts regardless of country studied and the classification of loneliness used [19]. One possible explanation for the greater loneliness experienced by older women may be that they are more willing to admit to socially unacceptable feelings than men [1], and that disclosing loneliness may be more socially accepted in women than in men [26].

Loneliness was shown to be independently associated with cardiovascular mortality in women only. A higher proportion of women (30.9%) reported being lonely relative to men (17.1%), and only 41 men reported being lonely. The lack of associations found between loneliness and subsequent mortality (both cardiovascular and all-cause) among men may thus be due to the smaller sample size and lower statistical power. With the exception of the study by Elovainio M, *et. al.*[4], most previous studies did not analyze men and women separately, and considered all-cause mortality only [5-11], making it difficult to compare with our study results. Findings across previous studies are inconsistent as to whether loneliness independently predicts mortality risk after adjusting for initial health status, health behaviors, depression, and other social factors. For instance, using UK biobank data on 466 901 men and women, the Elovainio M, *et. al.* study [4] reported that loneliness was not independently associated with either all-cause or cardiovascular mortality for both genders in multivariable adjusted models. Studying only all-cause mortality, similar findings have been reported by studies conducted in Amsterdam [6], France [5], England [8], and China [7]. Two studies conducted in the USA, however, reported that loneliness was an independent predictor of all-cause mortality after adjusting for prior health and health behavior and depression [10, 11]. The inconsistent findings across studies may be related to varying study designs, methods and follow-up periods. Possible mechanisms by which loneliness contribute to cardiovascular mortality may be that loneliness affects cardiovascular health by altering biomarkers and shaping health behavior that are associated with increased CVD risks. For example, loneliness has been associated with elevated blood pressure [18], elevated triglycerides level [20], smoking [19], and physical inactivity [19]. In our study, no association was found in women between loneliness and baseline SBP, DBP, triglyceride level or most of the prior health variables including smoking and physical activity. However, women with loneliness more often reported poor economy, chronic bronchitis, and living alone, and were more often diagnosed with depression, compared to those without loneliness. Loneliness predicted cardiovascular mortality in women after adjusting for the associated factors suggesting that loneliness alters physiology at a more fundamental level. Future research should include efforts to examine how physiological processes contribute to the effect of loneliness on mortality.

In conclusion, we found that loneliness was an independent predictor of cardiovascular mortality in women, while there was no evidence to indicate that loneliness was associated with an increased risk of either cardiovascular- or all-cause mortality in men. Our results emphasizes the importance of considering women with loneliness as a high-risk group to target *for* public health and medical care efforts in reducing cardiovascular mortality.

Declarations

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Authors' contributions

MN and IS designed the study. MN ran all the analyses, interpreted the results, and wrote the first draft of the manuscript. All authors revised the draft critically and have approved the final text.

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Availability of data and materials

The data supporting this article can be made available from the corresponding author on reasonable request.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Consent for publication

Consent for publication does not apply for this manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

1. Peplau LA, Perman D. Loneliness: A sourcebook of current theory, research and therapy. In: Peplau LA, Perman D, editors. *Perspective on loneliness*. New York: Wiley; 1982. p. 1-8.
2. Pinquart M, Sorensen S. Influences on Loneliness in Older Adults: A Meta-Analysis. *Basic and Applied Social Psychology*. 2001;23(4):245-66.
3. Anthony DO, Bert NU, Elaine W. Loneliness and Health in Older Adults: A Mini-Review and Synthesis. *Gerontology*. 2016;(62):443–9. doi: DOI: 10.1159/000441651.
4. Marko E, Christian H, Laura P, Marianna V, Kim J, Markus J, et al. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. *Lancet Public Health*. 2017;2:e260–66.
5. Maturin TT, Nadine ST, Ralitsa S, Céline M, Mélanie C, Hélène A, et al. Feelings of Loneliness and Living Alone as Predictors of Mortality in the Elderly: The PAQUID Study. *Psychosomatic Medicine* 2016;**78**:904-9.
6. Tjalling JH, Theo GT, Dorly JHD, Natasja S, Rien V, Jack D, et al. Impact of loneliness and depression on mortality: results from the Longitudinal Ageing Study Amsterdam. *The British Journal of Psychiatry*. 2016;209:127–34. doi: doi: 10.1192/bjp.bp.115.168005.
7. Luo Y, Waite LJ. Loneliness and mortality among older adults in China. *J Gerontol B Psychol Sci Soc Sci*. 2014;(69):633–45.
8. Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. *PNAS*. 2013;110(15):5797-801.
9. Shiovitz-Ezra S, Ayalon L. Situational versus chronic loneliness as risk factors for all-cause mortality. *International Psychogeriatrics*. 2010;22(3):455-62.
10. Luo Y, Hawkey LC, Waite LJ, Cacioppo JT. Loneliness, health, and mortality in old age: a national longitudinal study. *Soc Sci Med*. 2012;(74):907–14.
11. Perissinotto CM, Stojacic CI, Covinsky KE. Loneliness in older persons: a predictor of functional decline and death. *Arch Intern Med*. 2012;172:1078–84.
12. Rinder L, Roupe S, Steen B, Svanborg A. Seventy-year-old people in Gothenburg. A population study in an industrialized Swedish city. *Acta Med Scand*. 1975;198:397–407.
13. Steen B, Djurfeldt H. The gerontological and geriatric population studies in Gothenburg, Sweden. *Z Gerontol* 1993;26:163–9.
14. Berg S. Psychological functioning in 70- and 75-year-old people. A study in an industrialized city. *Acta Psychiatr Scand Suppl*. 1980;288:1–47.
15. Eriksson BG, Mellstrom D, Svanborg A. Medical-social intervention in a 70-year-old Swedish population. A general presentation of methodological experience. *Compr Gerontol*. 1987;(1):49-56.
16. Rydberg Sterner T, Ahlner F, Blennow K, Dahlin-Ivanoff S, Falk H, Havstam Johansson L, et al. The Gothenburg H70 Birth cohort study 2014-16: design, methods and study population. *Eur J Epidemiol*. 2018. doi: 10.1007/s10654-018-0459-8. PubMed PMID: 30421322.

17. Bergh I, Steen G, Waern M, Johansson B, Oden A, Sjostrom B, et al. Pain and its relation to cognitive function and depressive symptoms: a Swedish population study of 70-year-old men and women. *J Pain Symptom Manage*. 2003;26:903–12.
18. Hawkey LC, Masi CM, Berry JD, Cacioppo JT. Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychology and Aging*. 2006; 21(1):152-64.
19. Jiska CM, Haim H, Yaffa L, Vera S. Correlates and predictors of loneliness in older-adults: a review of quantitative results informed by qualitative insights. *International Psychogeriatrics*. 2016;4(28):557–76. doi: doi:10.1017/S1041610215001532.
20. Sorkin D, Rook KS, Lu JL. Loneliness, lack of emotional support, lack of companionship, and the likelihood of having a heart condition in an elderly population. *Annals of Behavioral Medicine*. 2002; (24):290–8.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Arlington, VA: American Psychiatric Association, 2013.
22. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV TR*. Washington, DC: American Psychiatric Association, 2000.
23. Skoog I, Nilsson L, Landahl S, Steen B. Mental disorders and the use of psychotropic drugs in an 85-year-old urban population. *Int Psychogeriatrics*. 1993;(5):33-48.
24. van't Hof MA, Burema J. Assessment of bias in the SENECA study. *Eur J Clin Nutr*. 1996;50(Suppl 2):4-8.
25. Shiovitz-Ezra S, Ayalon L. Use of direct versus indirect approaches to measure loneliness in later life. *Res Aging*. 2012;34:572-91.
26. Borys S, Perlman D. Gender differences in loneliness. *Personality and Social Psychology Bulletin*. 1985;11:63-75.

Figures

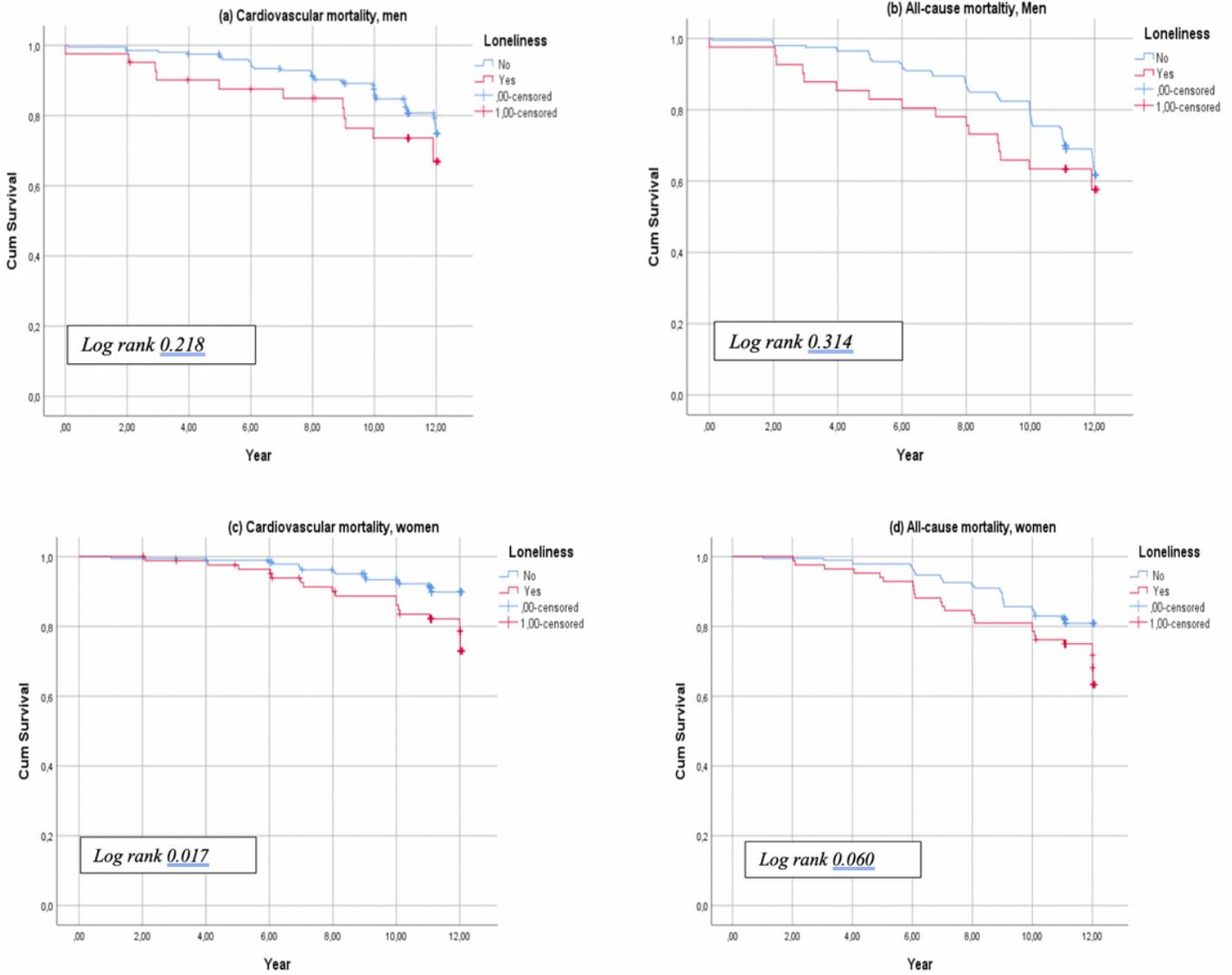
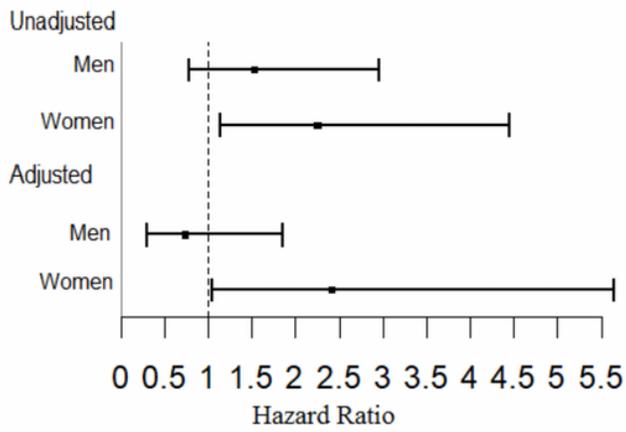


Figure 1

Kaplan-Meier survival estimates for 12-years follow-up according to perceived loneliness status for (a) cardiovascular mortality, men; (b) all-cause mortality, men; (c) cardiovascular mortality, women; and (d) all-cause mortality, women.

(a) Cardiovascular Mortality



(b) All-cause Mortality

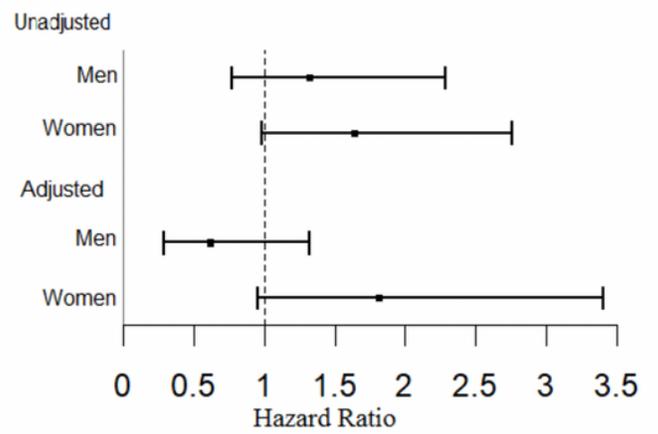


Figure 2

Cox proportional hazard ratios (HR) and 95% confidence intervals (CI) of (a) cardiovascular mortality and (b) all-cause mortality in men and women with loneliness.