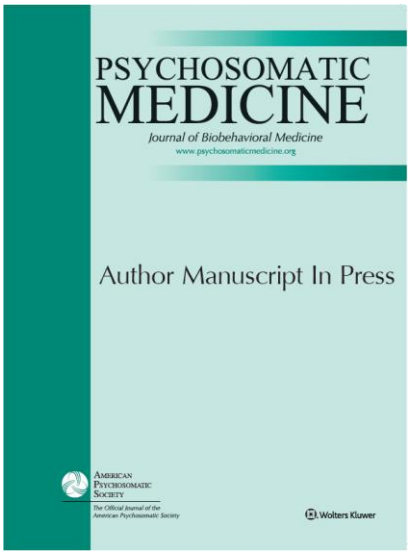

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Social isolation, Loneliness and All-cause Mortality in Patients with Cardiovascular Disease: A 10-year Follow-up Study

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Abstract

Objective: Social isolation and loneliness have been associated with increased incidence of cardiovascular disease (CVD), but few studies have evaluated the impact of social isolation and loneliness on mortality in people with existing CVD, and these are limited to Western populations. We examined whether social isolation and loneliness associated with increased risk of mortality in individuals with established CVD in Taiwan.

Methods: The cohort was composed of 1,267 patients with confirmed CVD aged 65 years or older followed up for up to 10 years. Cox proportional hazard regression models were used to examine the association between social isolation and loneliness at baseline and mortality at follow-up by adjusting for demographic variables, health-related behaviors, and health status.

Results: There were 593 deaths over the follow-up period. Social isolation was associated with increased risk of mortality after accounting for established risk factors (hazard ratio [HR]=1.16; 95% CI=1.06, 1.26), while loneliness was not associated with increased risk of mortality (HR=0.95; 95% CI=0.82, 1.09). When both social isolation and loneliness were included in the model, social isolation maintained an association with mortality (HR=1.16; 95% CI =1.07, 1.27).

Conclusions: Social isolation is associated with an increased risk of mortality in patients with CVD, and the effects are independent of loneliness. These findings expand our knowledge about the impact of social isolation on the outcomes of CVD in non-Western countries. Efforts to reduce isolation may have substantial benefits in terms of mortality in patients with CVD.

Keywords social isolation; loneliness; all-cause mortality; cardiovascular disease (CVD)

ADL= activities of daily living, **AMI**=acute myocardial infarction, **BMI**=body mass index, **CES-D**=Center for Epidemiologic Studies Depression Scale, **CHD**=coronary heart disease, **CVD**=cardiovascular disease, **HR**= hazard ratio, **ICD-9-CM**=*International Classification of Diseases, 9th Revision, Clinical Modification*, **NHIS**=National Health Interview Survey

Introduction

Social isolation and loneliness are reflections of the objective and subjective characteristics of impoverished social relationships respectively (1). Social isolation is a state of estrangement, which refers to the loss of social connection to other individuals and social organizations. Loneliness by contrast is a subjective feeling of distress, arising when there is a discrepancy between desired and actual social relationships (2). Although social isolation and loneliness tend to occur together, they can also be experienced independently of one another. This is supported by research showing that being alone and loneliness are only moderately correlated (3).

Substantial evidence suggests that high levels of social isolation or loneliness are associated with increased all-cause mortality risk in older adults (4-8). The risk associated with poor social connections is comparable with well-established risk factors for death, such as smoking, physical inactivity or obesity (9, 10). Research has also been conducted to identify the possible psychological and biological pathways through which social isolation and loneliness lead to poorer health and increased mortality (11-13).

Cardiovascular disease (CVD), including stroke and coronary heart disease (CHD), is the leading cause of death and disability worldwide (14). People who survive an acute cardiovascular event are at an increased risk of a subsequent cardiac event and premature death (15), making it important to explore psychosocial determinants in this high risk group. Both social isolation (16, 17) and loneliness (18, 19) have been prospectively related to a higher incidence of CVD in previous studies, and the results of one recent meta-analysis support the hypothesis that loneliness and social isolation are risk factors for the development of CVD (20). Their findings showed that poor social relationships were associated with a 29%

increase in the risk of CHD and a 32% increase in the risk of stroke. However, most of the previous studies were focused on the influence of social isolation or loneliness on the incidence of CVD rather than outcomes such as cardiac or total mortality in people with CVD. Although risk factors such as depression (21) and physical inactivity (22) have been associated with poorer outcomes among individuals with pre-existing CVD, only a few studies have examined the impact of social isolation or loneliness on the prognosis of CVD and results have been mixed. Williams and colleagues assessed social support in a cohort of patients with significant coronary artery disease. They reported that unmarried individuals without a close confidant had an adjusted hazard ratio for survival of 3.34 compared with those reporting either or both (23). A study of more than 450,000 people in the UK found that social isolation and loneliness were associated with increased risk of acute myocardial infarction (AMI) and stroke, but that only social isolation was related to subsequent mortality (24). Although this was a large-scale study with long-term follow-up, it only included participants aged between 40 and 69, limiting generalization beyond this age range.

Meanwhile, another gap in knowledge is the lack of studies on the health consequences of social isolation and loneliness in non-Western countries. Most studies on this topic have been conducted in North America and European countries (20), and it is not established whether similar patterns occur in other cultures. The importance of such research is underscored by the fact that isolation and loneliness are equally prevalent in non-Western as in Western countries. One study in China using national samples showed that 29.8% of older adults felt lonely (25). Another study in Japan showed that the prevalence of social isolation was 31.0% for older adults living alone and 24.1% for those living with family (26). Whether isolation and loneliness have similar health effects and operate through similar mechanisms in non-Western cultures remains to be studied. It has been suggested that the association

between social relationships and health could be more salient in Chinese populations, for whom cultural tradition emphasizes the family system and collectivism (25). However, little was known about the consequences of isolation and loneliness for the mortality of general Chinese population, not to mention the subgroup of patients with CVD. We therefore sought to investigate the associations of both subjective and objective deficiencies in social relationships with all-cause mortality in patients with CVD age 65 years or older in Taiwan. We conducted a prospective analysis to answer the following primary question: are social isolation and loneliness associated with increased mortality in patients with CVD? Another objective of our study is investigating whether loneliness or social isolation are differentially associated with all-cause mortality in patients with CVD.

Methods

Participants

This analysis used data from the 2005 National Health Interview Survey (NHIS) in Taiwan. The NHIS was conducted by the Ministry of Health and Social Welfare and the National Health Research Institutes in Taiwan. Participants were selected using a multi-stage stratified systematic sampling procedure to obtain a nationally representative sample.

The NHIS comprised 24,726 persons in Taiwan (response rate=80.59%). For this study, the NHIS data were combined with the 2003-2015 claims data in the National Health Insurance Research Database. National Health Insurance is a public compulsory insurance system in Taiwan that covered approximately 99.6% of the total population of over 23.6 million in 2017 (Ref: Ministry of Health and Welfare (2018). 2016-2017 National Health Insurance Annual Report. Taipei: Ministry of Health and Welfare).

Figure 1

Of all the 2005 NHIS participants age 65 years or older (n= 2,727), 1,760 participants consented to linkage of their survey data with National Health Insurance claims data. Among these participants, 1,267 who met the criteria for CVD at baseline were identified for the current study (see Figure 1). Two criteria for CVD included: (i) participants had at least one service claim between 2003 and 2005 for either outpatient or inpatient care with a principal diagnosis of CVD (The International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 390-438); and (ii) participants had at least one service claim for inpatient care or at least three services for outpatient care with a principal diagnosis of CVD between 2003 and 2015(27). The ethics protocol was approved by Taichung Veterans General Hospital Institutional Review Board, Taiwan (reference number: CE17201-1).

Measures

Survival status

Survival status for the period from 2005 to 2015 was assessed by matching personal identification numbers with the National Death Registry files provided by the Ministry of Health and Social Welfare, Taiwan.

Social isolation

We used an index comprised of different aspects of the social network. Six items were combined to create an index of social isolation, which was adapted from previous research (5, 12, 28). One point was assigned if participants were not married (never married, separated, divorced, widowed), living alone, had less than monthly contact with their children, and friends, and if they did not participate in any volunteer work or social groups (social clubs,

resident groups or religious groups) in the last three months. This resulted in a scale ranging from 0 to 6. Continuous isolation scores were used in the main analysis. For illustrative purposes, participants was categorized into two groups by the top quartile ($\geqslant$4 versus <4 points to indicate high versus low level of social isolation) (5).

Loneliness

Loneliness was measured with one single item from the Chinese version of Center for Epidemiologic Studies Depression Scale (CES-D). Participants were asked, "In the last week, have you experienced loneliness (felt isolated, with no companions)?", which was scored on a scale of 0 to 3, corresponding to responses of 'never', 'rarely', 'sometimes', and 'often'. All those participants who responded 'sometimes' or 'often' were classified as "lonely", those who responded 'never' or 'rarely' were classified as "not lonely". This measure has been used in a number of previous studies (4, 29-31).

Covariates

Covariates included demographic characteristics, lifestyles behaviors, health status, and comorbid conditions. All variables were provided by the 2005 NHIS. The following factors were selected as covariates based on previous research (5, 24): (1) socio-demographic characteristics including age, sex, education attainment, working status, monthly income. Marital status and living arrangement were not included as covariates since they were used to calculate the index of social isolation; (2) lifestyle behaviours: smoking status (current smoker, former smoker, and never smoked), alcohol consumption (yes vs. no), physical activity expenditure was computed by activity intensity code (kcal/min)×frequency per week (times)×duration for each time (min), which was classified into four categories (0, 1–999, 1,000–1,999 and ≥2,000 kcal/week)(32); (3) health and chronic conditions: body mass index

(BMI: <18.5, 18.5-23.9, 24-26.9, and ≥27) (33), difficulty with activities of daily living (ADL), and Charlson comorbidity index, which was calculated based on the number and severity of chronic conditions (34). Depressive symptoms were measured by the Chinese version of CES-D, a 10-item questionnaire with good reliability and validity (35-37). The CES-D scoring was revised to exclude the loneliness question in order to derive a depression score that was calculated as the sum of the remaining nine questions (possible range 0–9).

Statistical analysis

Descriptive statistics ($\chi 2$) for all-cause mortality were calculated first to characterize baseline data. Variables with a *P*-value <0.25 were included in the subsequent Cox proportional hazard models for adjustment since using the conventional level (such as 0.05) may fail to identify variables known to be important (38). The associations between isolation, loneliness and depressive symptoms were tested using Pearson correlations.

The associations between social isolation, loneliness and mortality (when adjusting for other variables) were calculated using separate Cox proportional hazard regression models. Three models were fitted. Model 1 was constructed to examine the associations between social isolation at baseline and mortality at follow-up by adjusting for demographic variables, health-related behaviors, and health status. A similar model was fitted to test the independent association of loneliness on mortality (Model 2). Model 3 was conducted by adding both social isolation and loneliness into the fully adjusted model. We also tested whether there was an interaction effect between social isolation and loneliness on mortality by adding appropriate interaction terms into the model. Kaplan–Meier survival curves were plotted to examine differences in cumulative survival across categories of social isolation and differences were compared with log-rank statistics.

A sensitivity analysis was carried out to prevent the possibility that associations were caused by individuals having become isolated or lonely as a consequence of illness. Participants who had died within the first 2 years after baseline (2005-2007) were excluded from the analysis.

All data access and statistical analyses were performed in the Health and Welfare Data Science Centre, Taiwan Ministry of Health and Welfare to ensure an adequate level of data protection. All analyses were conducted using SAS 9.4 software and a P value < 0.05 was considered statistically significant.

Results

We carried out analyses on 1,267 participants with CVD at the baseline, tracking mortality until December 2015. A total of 593 people died (46.8%), of whom 334 were men (56.3%). The mean score (SD) of social isolation and loneliness for this sample was 2.6 (1.2) and 0.4 (0.7) respectively. We defined social isolation and loneliness as having a score within the top quartile, with 23.2% of the participants categorized as socially isolated and 24.2% categorized as lonely. Social isolation and loneliness were positively correlated (r = 0.21, P < 0.001), and depressive symptom scores were positively correlated with social isolation (r = 0.22, P < 0.001) and loneliness (r = 0.54, P < 0.001).

Table 1

The baseline characteristics are shown in Table 1. In relation to all-cause mortality, there was statistical significance for all variables except for alcohol consumption and loneliness. All-cause mortality was higher in men and was associated with older age, less education and

lower income. It was also associated with a range of health status and comorbid conditions. Social isolation was associated with all-cause mortality; the absolute proportions of deaths were 65.0 vs. 41.3% in the high and low isolation groups.

Table 2

The fully adjusted multivariable regression models (Table 2) show that patients with CVD who had a higher level of social isolation had a significantly increased risk of all-cause mortality, compared to individuals with a lower level of social isolation (HR=1.16; 95% CI=1.06, 1.26) (Model 1). Loneliness by contrast was not associated with mortality among participants with CVD (HR=0.95; 95% CI=0.82, 1.09) (Model 2). Adding loneliness to the model did not reduce the HR for social isolation (HR=1.16; 95% CI=1.07, 1.27). The interaction terms between social isolation and loneliness were not statistically significant (*P* for interaction=0.75), indicating that there was no synergistic effect between social isolation and loneliness on mortality. Survival curves for all-cause mortality across categories of social isolation are presented in Figure 2. Increasing social isolation was associated with increased mortality risk (log-rank $\chi^2 = 69.01$, df = 1, $P < 0.001$).

Figure 2

We carried out a sensitivity analysis to test possible reverse causality, by repeating the analysis after excluding death within 2 years of follow-up. The results are comparable to those in the main analysis. The HR for social isolation remained significant in the fully adjusted model (isolation: HR= 1.20, 95% CI= 1.09-1.32, $P < 0.001$; loneliness: HR= 0.99, 95% CI= 0.84-1.16, $P = 0.86$)

Discussion

In this study of older adults aged⩾65 years in Taiwan, we found that social isolation predicted mortality over a 10-year follow-up period in patients with CVD. The association between social isolation and mortality was independent of demographic factors and baseline health status. Our results suggest that loneliness, the subjective experience of social disconnection, appears not be involved in the association between social isolation and mortality. These findings expand our knowledge about the impact of social isolation on the outcomes of CVD in populations other than in the Western countries. Previous studies have indicated that both social isolation and loneliness are associated with increased all-cause and cardiovascular disease mortality (6, 9), although there are variations in the extent to which both factors are relevant. Differences between our findings and previous results could be related to study design or to selective publishing of positive results, as has been suggested in one meta-analysis (20). It is possible that loneliness is associated with other risk factors, so that in multivariable analysis it does not emerge as an independent risk factor. Two studies with older adults in Western countries both found that the associations between loneliness and all-cause mortality were no longer significant after baseline health, functional limitations, and depressive symptoms were taken into account (5, 39). Our results are consistent with another recent report of a large population-based study in the UK, where results also indicated that social isolation rather than loneliness predicted mortality in patients with MI and stroke (24). No significant interaction effects were detected between social isolation and loneliness in our study, which was also consistent with previous findings in Western countries (5, 24, 40). Taken together, these findings suggest that social isolation, along with other risk factors such as depression and low physical activity, can be regarded as a risk factor for poor prognosis of individuals with CVD.

If the adverse effects of social isolation on the mortality of patients with CVD cannot be explained by the psychological process integral to loneliness, alternative mechanisms must exist. First, social contact itself may have specific biological consequences that are important for health maintenance. A growing literature indicates that low-quality social relationships are associated with poorer biological profiles, including elevated blood pressure, metabolic dysfunction, and raised levels of inflammation and stress hormones (13, 41-43). Second, social isolation may affect cardiac outcomes via promoting unhealthy lifestyles. In a recent longitudinal study among older English adults, social isolation was found to be associated with a wide range of health-damaging behaviors including smoking, low physical activity, and poor dietary habit, while loneliness was not associated with any persistent health-related behaviors (44). Third, people who live alone or lack social contacts may be at increased risk of death because acute symptoms may develop when they are alone, or because they have smaller networks of individuals who can help them secure prompt medical attention (45).

Although our study had a prospective design, the possibility of reverse causality deserves attention. Social isolation may be more common in people who are seriously ill, so the observation of greater mortality might reflect more serious illness rather than isolation per se. This possibility cannot be ruled out completely, although we repeated the analysis by excluding participants who died within 2 years of follow-up, and the results were very similar to those for the full cohort. However, it is possible that some other unmeasured factors were responsible for the findings.

The strengths of this analysis include the longitudinal design with a representative population cohort in which it was possible to adjust for multiple health and demographic factors. We were also able to construct a comprehensive social isolation index that included

contacts with friends, relatives, and family as well as social participation. But there are several methodological limitations worth noting. First, loneliness was assessed with only one direct question regarding the perception of loneliness in the last week. Despite wide use in the literature and strong correlations with several established multiple-item scales, this measure may be less reliable than a composite measure that taps multiple aspects of loneliness (46-48). Moreover, the single item loneliness measure might be more prone to social desirability bias than more indirect questions about loneliness, because people may be unwilling to admit to feeling "lonely" (49). This could be especially true for samples from collectivist cultures that value interdependence, mutual support, and common goals. Although we measured loneliness in a simple way, another study using a more complex measure have reported similar findings (50). In this 25-year study, loneliness was assessed four times using a validated 11-item questionnaire, but no independent association between loneliness and risk of all-cause, cardiovascular and non-cardiovascular death was found. Second, although we adjusted for a comprehensive set of variables, our study does not prove that social isolation contributes directly to mortality. Future studies should test the possible mediating effects of variables such as smoking, low physical activity and poor mental health on this association. There is also a possibility that the outcomes may be accounted for in part by other confounding variables which were not assessed, such as personality and coping styles.

The findings of this study confirm that social isolation is associated with higher mortality in patients with CVD but indicate that this effect is independent of the emotional experience of loneliness. Reducing both social isolation and loneliness are important for quality of life and well-being, but efforts to reduce isolation would be likely to have greater benefits in terms of mortality in patients with CVD.

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Captions for the figures

Figure 1 Flow chart of the selection of analytical sample

Figure 2 Survival curve for all-cause mortality in patients with cardiovascular disease (n=1,267) according to social isolation categories: National Health Interview Survey (NHIS) in Taiwan, 2005-2015

Figure 1

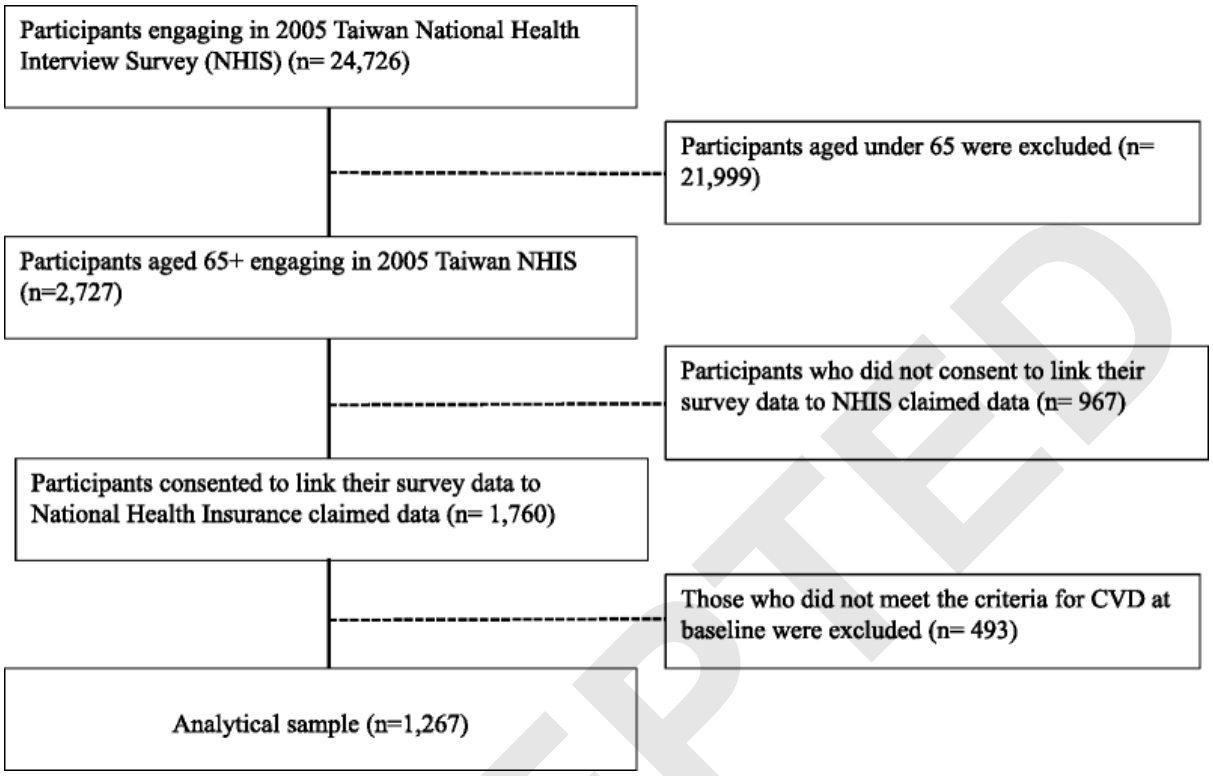

Figure 2

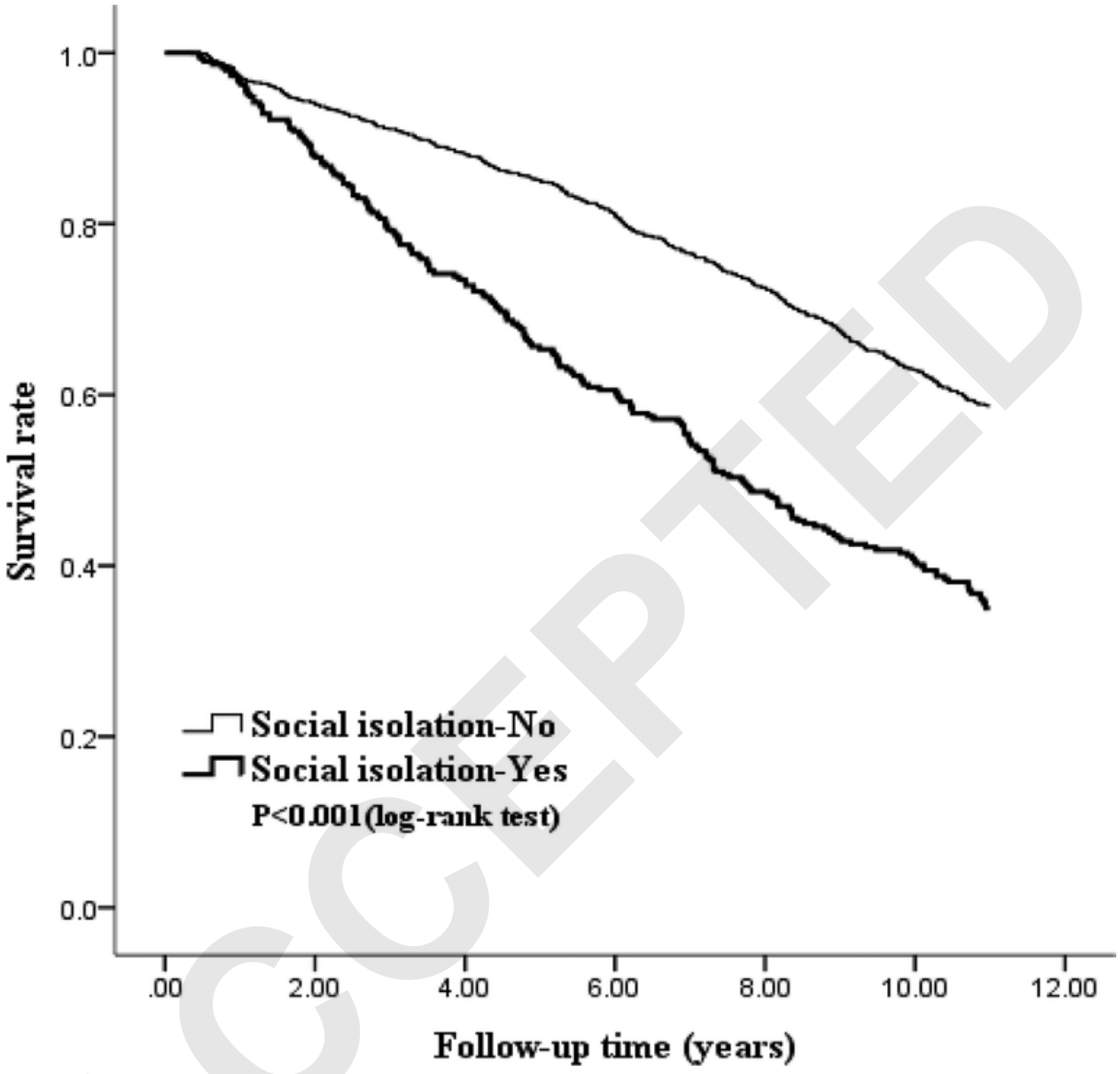

Table 1. Characteristics and mortality in Taiwan-based sample of patients with cardiovascular disease (n=1,267)

Variables in 2005	N	All-cause mortality		p-value[a]
		n	%	
Sex				<0.001
Female	622	259	(41.6)	
Male	645	334	(51.8)	
Age				<0.001
65-74	719	230	(32.0)	
75+	548	363	(66.2)	
Education				<0.001
No formal schooling	453	246	(54.3)	
Elementary school+	811	344	(42.4)	
Body mass index (kg/m^2)				<0.001
<18.5	65	45	(69.2)	
27+	268	111	(41.4)	
24–26.99	345	133	(38.6)	

18.5–23.99	547	270	(49.4)	
Smoker				<0.001
Current	184	108	(58.7)	
Former	162	90	(55.6)	
Never	896	382	(42.6)	
Alcohol consumer				0.207
Yes	230	99	(43.0)	
No	1037	494	(47.6)	
Total PA energy expenditure				<0.001
(kcal/week)				
0	462	285	(61.7)	
1–999	354	160	(45.2)	
1000–1999	190	60	(31.6)	
2000+	261	88	(33.7)	
Charlson comorbidity index				<0.001
≧3	305	196	(64.3)	

1–2	580	260	(44.8)	
0	382	137	(35.9)	
Depressive symptoms (10-item CES-D)				0.009
<10	926	380	(41.0)	
≧10	225	114	(50.7)	
Social Isolation				<0.001
No(<4)	973	402	(41.3)	
Yes(≧4)	294	191	(65.0)	
Loneliness				0.111
No	844	350	(41.5)	
Yes	306	143	(46.7)	

a: Chi-square tests

Table 2. Results of Cox proportional hazards model for estimating the multivariable association of social isolation and loneliness with all-cause mortality in patients with cardiovascular disease (n=1,097)

Variables	All-cause mortality								
	Model 1 Social isolation			Model 2 Loneliness			Model 3 Social isolation+loneliness		
	HRs	95% CI	*p*	HRs	95% CI	*p*	HRs	95% CI	*p*
Social isolation	1.16	(1.06-1.26)	0.001	–	–	–	1.16	(1.07-1.27)	0.001
Loneliness	–	–	–	0.95	(0.82-1.09)	0.428	0.92	(0.80-1.06)	0.240
Sex									
Female	1.00	–	–	1.00	–	–	1.00	–	–
Male	1.56	(1.21-2.00)	0.001	1.55	(1.20-1.99)	0.001	1.57	(1.22-2.01)	<0.001
Age									
65-74	1.00	–	–	1.00	–	–	1.00	–	–
75+	2.16	(1.78-2.64)	<0.001	2.32	(1.91-2.82)	<0.001	2.17	(1.78-2.64)	<0.001
Education									
No formal schooling	1.00	–	–	1.00	–	–	1.00	–	–

Elementary school+	0.73	(0.59-0.90)	0.004	0.70	(0.57-0.86)	0.001	0.73	(0.60-0.91)	0.004
Body mass index (kg/m^2)									
<18.5	1.00	–	–	1.00	–	–	1.00	–	–
18.5–23.99	0.81	(0.53-1.24)	0.337	0.83	(0.54-1.27)	0.393	0.81	(0.53-1.25)	0.345
24–26.99	0.63	(0.40-0.99)	0.044	0.65	(0.41-1.01)	0.058	0.63	(0.40-0.99)	0.045
27+	0.70	(0.44-1.12)	0.135	0.72	(0.45-1.15)	0.170	0.70	(0.44-1.12)	0.134
Smoker									
Current	1.00	–	–	1.00	–	–	1.00	–	–
Former	0.84	(0.61-1.14)	0.254	0.85	(0.63-1.16)	0.311	0.84	(0.61-1.14)	0.254
Never	0.64	(0.48-0.84)	0.001	0.64	(0.49-0.85)	0.002	0.64	(0.48-0.84)	0.001
Alcohol consumer									
Yes	1.00	–	–	1.00	–	–	1.00	–	–
No	1.21	(0.94-1.56)	0.139	1.24	(0.96-1.59)	0.101	1.22	(0.95-1.58)	0.118
Total PA energy expenditure (kcal/week)									
0	1.00	–	–	1.00	–	–	1.00	–	–

1–999	0.87	(0.70-1.09)	0.233	0.87	(0.70-1.10)	0.243	0.88	(0.70-1.10)	0.247
1000–1999	0.59	(0.44-0.81)	0.001	0.59	(0.43-0.80)	0.001	0.59	(0.44-0.81)	0.001
2000+	0.62	(0.47-0.82)	0.001	0.60	(0.46-0.80)	<0.001	0.62	(0.47-0.82)	0.001
Charlson comorbidity index									
≧3	1.00	–	–	1.00	–	–	1.00	–	–
1–2	0.70	(0.56-0.87)	0.001	0.70	(0.56-0.88)	0.002	0.70	(0.56-0.87)	0.002
0	0.56	(0.43-0.73)	<0.001	0.58	(0.44-0.75)	<0.001	0.56	(0.43-0.73)	<0.001
Depressive symptoms scores[a]	1.02	(1.00-1.04)	0.027	1.03	(1.01-1.06)	0.003	1.03	(1.01-1.05)	0.012

CI: confidence intervals; PA: physical activity

[a]: Depressive symptoms scores were computed based on the 9 items of CES-D without including the loneliness question.