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1 **Exploring the effect of loneliness on all-cause mortality in Spain: are**

2 **there differences between older adults and young- and middle-aged**

3 **adults?**

4

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ABSTRACT

This study aims to investigate the effect of loneliness on all-cause mortality over a 6-year follow-up period using the overall sample and by age groups (18-59 years and 60+ years). Data from a longitudinal, prospective study of a nationally-representative sample of the Spanish non-institutionalized adult population were analysed (n=4,467). Mortality was ascertained via linkage to the National Death Index or obtained during the household visits. The 3-item UCLA Loneliness Scale was used to measure loneliness. Sex, age, education, physical activity, tobacco consumption, body mass index, disability, depression, living situation, and social participation were also considered as covariates. Multivariable Cox proportional hazard models were carried out. Higher level of loneliness was not associated with mortality risk in fully covariate-adjusted models over the entire population (HR=1.02; 95% CI=0.94, 1.12). The interaction effect between loneliness and age groups was significant, indicating that the rate for survival of loneliness varied by age (HR=1.29; 95% CI=1.02, 1.63 for young- and middle-aged individuals; HR=0.96; 95% CI=0.89, 1.04 for older adults). The development of interventions aimed at tackling loneliness among young- and middle-aged adults might contribute to mortality risk reduction. Future research is warranted to test whether our results may be replicated.

Keywords: Spain; loneliness; all-cause mortality; population-based study; age differences.

Introduction

Loneliness refers to a distressing perceived discrepancy between one´s social desires and one´s actual interactions with others (Perlman & Peplau, 1981). Variations in lifestyle, social networks and support (e.g. increases in divorce rates, increasing use of digital tools for communication, rising number of individuals living alone), together with the number of older people rising faster than ever (United Nations, 2019) might be among the reasons why individuals are experiencing loneliness.

A variety of studies have shown the impact of loneliness on diverse adverse health outcomes (Honigh-de Vlaming et al., 2014; Lara et al., 2019; Matthews et al., 2016; Rico-Uribe et al., 2016). The extent to which loneliness is of public health relevance has ultimately led to a plethora of research on mortality over the last twenty years. A meta-analysis of 70 prospective studies including more than three million participants found evidence that loneliness increases the risk of premature death, with comparable magnitude of effects against other well-known lifestyle risk factors (Holt-Lunstad et al., 2015). However, most of these studies included a limited set of confounding factors. Indeed, among the few ones in which loneliness was evaluated together with factors that might confound the above-mentioned relationship, the evidence suggested that this association could be fully attributable to other socioeconomic, lifestyle, and health factors (Elovainio et al., 2017; Hakulinen et al., 2018; Iecovich et al., 2011; Steptoe et al., 2013a). Moreover, prior data has been collected within Anglo-Saxon, Asian and Nordic countries so far, regardless of the apparent differences between these and the Mediterranean context in terms of the social interactions (Hansen & Slagsvold, 2015).

Despite older adults are being perceived as especially vulnerable to loneliness, this problem can occur at any point in life. Previous research has even suggested that the older population tend to report slightly less feelings of loneliness than young- and middle-

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aged individuals (d'Hombres et al., 2018), although there is also empirical evidence
showing a curvilinear figure between loneliness and age (Yang & Victor, 2011). Whereas
there are extensive data on the association between loneliness and mortality in the older
population, the study on younger cohorts is currently lacking. Therefore, the aims of this
study are: i) To investigate the effect of loneliness on all-cause mortality while adjusting
for a wide range of covariates over a 6-year follow-up period in a nationally-
representative sample of Spanish adults; and ii) To explore the extent to which the
potential association between loneliness and mortality varied between young- and
middle-aged adults vs older adults.

Material and methods

The survey

Data from a longitudinal, prospective study of a nationally representative sample of the
Spanish non-institutionalized adult population were analysed. The baseline survey (wave
1) was part of the Collaborative Research on Ageing in Europe (COURAGE in Europe)
study and was conducted between 2011 and 2012. First (wave 2) and second (wave 3)
follow-up examinations were collected as part of the *Edad con Salud* project between
2014 and 2018 at intervals of approximately 3 years.

Respondents were selected by a stratified, multistage, clustered area probability
design, according to the geographical areas and population size. Data on households were
provided by the Spanish Statistical Office. The study protocol was reviewed and approved
by the Ethics Review Committees of Parc Sanitari Sant Joan de Déu, Barcelona, and
Hospital Universitario La Princesa, Madrid.

Details on data collection procedures have been described elsewhere (Garin et al.,
2014). In brief, respondents underwent in-home computer-assisted interviews and a
standardized health examination including neuropsychological tests. If participants were

107   unable to undertake the interview because of severe cognitive impairment or physical

108   limitations, a shorter version of the questionnaire was administered to a proxy respondent.

109   A total of 4,753 individuals were initially interviewed at baseline (response

110   rate=69.9%). For the present study, those who participated at the baseline survey via a

111   proxy respondent (n=170) or those with missing values on loneliness (n=116) were

112   excluded, leaving a final analytical sample of 4,467 individuals. Informed consent was

113   obtained from all respondents.

114   ***Measures***

115   *Mortality*

116   Vital status and date of death were ascertained via linkage to the National Death Index.

117   Additionally, information on vital status was obtained during the household visits and in

118   case the participant had passed away, a verbal autopsy questionnaire (Kowal et al., 2012)

119   was administered to a next of kin or another caregiver. For those deceased participants

120   with insufficient data (n=21), date of death was assumed to have occurred at the midpoint

121   between the last follow-up and the next data collection period.

122   *Loneliness*

123   The three-item UCLA Loneliness Scale (Hughes et al., 2004) was used to measure

124   loneliness. Items were assessed on a three-point scale (1=hardly ever; 2=some of the time;

125   3=often). Responses were added up to produce a loneliness score ranging from 3 to 9,

126   with higher values indicating higher level of loneliness.

127   *Covariates*

128   Sociodemographic confounders included sex, age (in years), education (in years) and

129   information on the living situation (i.e. living alone vs living with other people). The

130   physical activity level was assessed by means of the Global Physical Activity

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131 Questionnaire (GPAQ) version 2 (Bull et al., 2009) and classified as low, moderate or

132 high (World Health Organization, 2012). Data on tobacco consumption (never, former or

133 current smokers) were also collected. Body mass index (BMI) was calculated as the

134 weight in kilograms divided by the square of the height in metres (kg/m2). Disability was

135 assessed with the 12-item version of the World Health Organization Disability

136 Assessment Schedule 2.0 (Üstün et al., 2010). An Item Response Theory approach was

137 used, transforming the resulting latent scores to a 0-100 scale, with 0 indicating minimum

138 disability/best functioning ability and 100 indicating maximum disability/worst

139 functioning ability. Depression in the previous 12-months was assessed with an adapted

140 version of the Composite International Diagnostic Interview (CIDI 3.0) (Haro et al.,

141 2006). An algorithm based on the DSM-5 was used for the endorsement of a major

142 depressive episode (American Psychiatric Association, 2013). Finally, respondents were

143 asked about how often in the previous 12 months they participated in different social

144 activities including religious services, social meetings, activities, programs or events, and

145 friends or relatives' visits using a sum score of 11 questions ranging from 11 to 55. Higher

146 values represent greater social participation.

147 *Statistical analysis*

148 Descriptive analyses on the baseline sociodemographic and clinical characteristics of the

149 sample were performed.

150 Multivariable Cox proportional hazard models (Cox & Oakers, 1984) were

151 performed to evaluate the association of loneliness with risk of all-cause mortality.

152 Survival time was calculated on a daily basis: from the date of baseline interview to the

153 date of death. Respondents who did not die at the time of their last observational period

154 were censored. An adjusted model was constructed for loneliness and all the covariates

155 simultaneously. Covariates were included in the models as categorical with the exception

of age, education, BMI, disability, and social participation. We then added an interaction term between loneliness and age groups to the adjusted model. To interpret the effect of loneliness on survival time in the presence of interaction, subsequent adjusted models were conducted for each age group.

Survival functions were also constructed to illustrate differences in mortality risk for loneliness by age groups while keeping covariates at their means. For the sake of clarity, loneliness was defined as a categorical variable using a cut-off score of 6 (Steptoe et al., 2013b).

Sensitivity analyses were carried out to examine the robustness of the main results by including the number of chronic conditions instead of disability as a covariate in the adjusted model. These chronic conditions were assessed through self-reported physician's diagnosis, symptom-based algorithms, and/or direct measurements [see Koyanagi et al. (2018) for details]. We additionally conducted multivariable analysis on a subsample of participants who survived for at least 365 days (n=4,210) to rule out the possibility of an association explained by reverse causality.

Analyses were weighted to account for the sampling design and to generate nationally representative estimates. Normalized weights were employed. Post-stratification corrections were made to the weights to adjust the sample to the Spanish sociodemographic distribution. For all regression analyses, complete case analyses were carried out. Results are presented as hazards ratios (HR) with their corresponding 95% confidence intervals (CIs). The level of statistical significance was set at $p<0.05$. Data analyses were performed using Stata 15.

Results

Baseline characteristics of the study sample according to survival status are provided in **Table 1**. In this sample of 4,467 individuals (2,108 aged 18-59 years; 2,359 60+ years),

181   442 (9.9%) participants died during a mean follow-up period of 6.4 years (SD=1.2).

182   Statistically significant differences were found in all study variables between deceased

183   and non-deceased participants, although effect sizes were small (except for age; Hedges'

184   *g*=1.56).

185   Adjusted results of the Cox regression analyses are illustrated in **Table 2**. Higher

186   level of loneliness was not associated with greater risk of mortality (HR=1.02; 95%

187   CI=0.94, 1.12). The interaction effect between loneliness and age groups was significant,

188   indicating that the rate for survival of loneliness varied by age (HR=0.73; 95 CI%=0.58,

189   0.90; Wald test χ^2(3, 139)=42.25, p<0.001). We then calculated differences in loneliness

190   in terms of survival by age groups (**Table 3**). For young- and middle-aged participants,

191   the higher level of loneliness, the worse negative effect on survival (HR=1.29; 95%

192   CI=1.02, 1.63). By contrast, increased loneliness was not associated with lower

193   probability of survival among individuals aged 60+ years (HR=0.96; 95% CI=0.89, 1.04).

194   Survival curves were also plotted from an adjusted Cox regression model that

195   included loneliness as a categorical variable (**Figure 1**). The probability of survival until

196   the end of the observational period was lower among those individuals reporting feelings

197   of loneliness in the young- and middle-aged groups. On the contrary, the mortality risk

198   did not vary by loneliness among participants aged 60+ years.

199   In sensitivity analysis including the number of chronic conditions as a covariate,

200   higher loneliness was significantly associated with increased risk of mortality only in the

201   younger-age group (HR=1.28; 95% CI=1.02, 1.61). After excluding individuals that

202   deceased during the first follow-up year, higher loneliness was also significantly

203   associated with decreased probability of survival in 18-59 years' individuals (HR=1.36;

204   95% CI=1.03, 01.81).

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Discussion

Data from a nationally representative sample of Spanish adults were used to investigate the longitudinal relationship between loneliness and mortality risk. Our results showed that loneliness was not related to all-cause mortality after adjusting for a wide range of confounding factors. However, we did find an interactive effect of loneliness and age groups on mortality. This study revealed a significant association between loneliness and mortality risk among young- and middle-aged participants, even after conducting sensitivity analyses.

In agreement with previous literature (Yang & Victor, 2011), this study found that older adults reported slightly higher feelings of loneliness. It is challenging to reconcile our results that loneliness is not associated with mortality risk among older adults with an important amount of evidence on the effects of loneliness on mortality (Holt-Lunstad et al., 2015; Rico-Uribe et al., 2018). However, prior works included a broad spectrum of different conceptual and measurement approaches, with insufficient or inconsistent inclusion of covariates, which may account for the observed heterogeneity.

Results point to the value of loneliness as predictor of mortality in young- and middle-aged adults. As far as we are aware, evidence of whether loneliness increased the risk of mortality specifically among the subpopulation of young- and middle-aged individuals is non-existent. It could be argued that younger cohorts exhibit a qualitatively different loneliness that is related with a need of higher frequency and intensity in their social interactions whereas emotionally meaningful social relationships acquire greater value among their older counterparts (Carstensen et al., 1999). In addition, it may be that the loneliness of young- and middle-aged individuals is associated with more harmful effects on health-related outcomes (Rico-Uribe et al., 2016). It is well-known that older individuals may be more vulnerable to experience loneliness due to retirement,

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231 bereavement or children leaving home (Wrzus et al., 2013). However, they could exhibit

232 a stronger capacity for managing and overcoming stressful events such as those

233 mentioned above in the view of resilience as a life-span process (Portella Fontes &

234 Liberalesso Neri, 2015). On the contrary, young- and middle-aged individuals, as they do

235 not expect encountering certain life-changing events at earlier stages of life, may find

236 more difficulties to cope with these situations. Either way, when the loneliness variable

237 was dichotomized to illustrate the survival function by age groups, the figure showed

238 slightly higher probability of mortality among young- and middle-aged individuals

239 reporting loneliness. We therefore caution the readers about the conclusions of this work.

240 Even if loneliness may well have significant effects on mortality in particular

241 subpopulations, our study suggests the necessity to add new evidence to confirm the

242 generalizability of the results found.

243　　Population trends and the growing research evidence that loneliness is influencing

244 a large number of health-related outcomes are predicted to shot up the public agenda.

245 Countrywide initiatives are gradually recognizing the importance of adequately

246 addressing this health challenge, whereas a sizeable amount of non-governmental

247 organizations are already implementing preventable actions and strategies to tackle

248 loneliness. Interventions have conventionally involved opportunities for social

249 interactions and the enhancement of social abilities for the older population, or the

250 youngest population at best, which cannot be criticised whatsoever. However, hardly any

251 of these organizations target the young- and middle-age groups. In view of our results,

252 programmes focused on younger populations might also have the potential to reduce

253 mortality risk.

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Strengths and limitations

The strengths of the study include the use of large nationally representative data, which allows for the simultaneous examination of multiple factors and greater ecological validity. Moreover, loneliness was measured by means of a questionnaire with satisfactory evidence of validity and reliability (Hughes et al., 2004).

This study presents several shortcomings. The loneliness variable has been artificially dichotomized for some specific analyses, which may result in loss of power. However, the positively skewed nature of the loneliness score suggests that this variable may fall into two groups. In addition, dichotomization was based on previous literature (Steptoe et al., 2013b) to aid in the interpretation of the findings. In addition, our findings have been skewed to the participants with longer survival, since those who were exposed to known risk factors for mortality may have died before the first assessment and participants who required a proxy respondent to participate were not included in the analytic sample. Thus, our results are limited to the relatively small number of participants who died within the six years after the baseline data collection. This is especially relevant among the younger age group, which may well have led to a biased estimation of the true association between loneliness and mortality.

Conclusions

Loneliness was not associated with higher risk of mortality over a 6-year follow-up period in a nationally representative sample of Spanish adults. However, loneliness was related to increased mortality risk in young- and middle-aged adults. The development of interventions aimed at tackling loneliness in subpopulations other than older adults might contribute to mortality risk reduction. Future research is warranted to test whether our results may be replicated.

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378 **Table 1.** Baseline sociodemographic and clinical characteristics according to survival
379 status.
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Characteristics	Total sample (n=4,467)	Deceased participants (n=442)	Alive participants (n=4,025)	p-value[b]	Effect size[c]
Sex				0.002	0.05
Female	50.9	41.3	51.5		
Male	49.1	58.7	48.5		
Age in years (mean, SD)	47.7 (17.7)	72.4 (19.7)	46.3 (16.4)	<0.001	1.56
Education in years (mean, SD)	12.8 (6.0)	8.6 (8.5)	13.1 (5.8)	<0.001	0.74
Physical activity				<0.001	0.12
Low	27.7	46.9	26.7		
Moderate	36.5	37.4	36.5		
High	35.7	15.7	36.9		
Tobacco consumption				<0.001	0.08
Non smokers	46.2	47.0	46.2		
Former smokers	19.6	22.4	34.8		
Current smokers	34.2	30.6	19.0		
Body mass index (mean, SD)	26.9 (4.9)	28.3 (7.3)	26.8 (4.8)	<0.001	0.29
Disability (mean, SD)	6.8 (14.2)	24.3 (34.9)	5.8 (12.3)	<0.001	1.15
Depression	8.9	16.4	8.4	<0.001	0.06
Living alone	15.9	28.6	15.2	<0.001	0.08
Loneliness (mean, SD)	3.7 (1.4)	4.1 (2.3)	3.6 (1.3)	<0.001	0.35
Social participation (mean, SD)	19.1 (5.5)	16.3 (10.2)	19.3 (5.2)	<0.001	0.51

381 *Note.* Values are percentages for each category unless otherwise indicated.
382 Abbreviations: SD=Standard Deviation.
383 [b] The difference between groups was tested by χ^2 tests and unpaired Student's *t*-tests for categorical and
384 continuous variables respectively.
385 [c] Cramer's *V* for χ^2 tests and Hedges' *g* for unpaired Student's *t*-tests. Effect size was reported for all the
386 differences that were found to be significant at the 95% confidence level.
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Table 2. Hazard ratios (95% CI) of the effect of loneliness and other covariates on all-cause-mortality.

	HR (95% CI)
	Adjusted
Loneliness	1.02 (0.94, 1.12)
Sex (ref. male)	0.42*** (0.28, 0.62)
Age (in years)	1.09*** (1.08, 1.11)
Education (in years)	0.99 (0.98, 1.02)
Physical activity (ref. high)	
Low	1.59* (1.01, 2.51)
Moderate	1.48 (0.99, 2.19)
Tobacco consumption (ref. non-smokers)	
Former smokers	1.13 (0.78, 1.64)
Current smokers	2.08** (1.34, 3.20)
Body Mass Index	0.98 (0.95, 1.03)
Disability	1.01*** (1.01, 1.02)
Depression	1.03 (0.56, 1.88)
Living alone (ref. no)	1.14 (0.78, 1.66)
Social participation	0.97* (0.94, 0.99)

Abbreviations: CI=Confidence Interval; HR= Hazard Ratio.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 3. Hazard ratios (95% CI) of the effect of loneliness on all-cause-mortality by age-groups.

	18-59 years		60+ years	
	HR (95% CI)		HR (95% CI)	
	Unadjusted	*Adjusted*	*Unadjusted*	*Adjusted*
Loneliness	1.40*** (1.18, 1.67)	1.29* (1.02, 1.63)	1.08 (0.99, 1.16)	0.96 (0.89, 1.04)

Abbreviations: CI=Confidence Interval; HR= Hazard Ratio.
Note= adjusted models include sex, age, education, physical activity, tobacco consumption, body mass index, disability, depression, living alone and social participation as covariates.
* $p < 0.05$; *** $p < 0.001$.
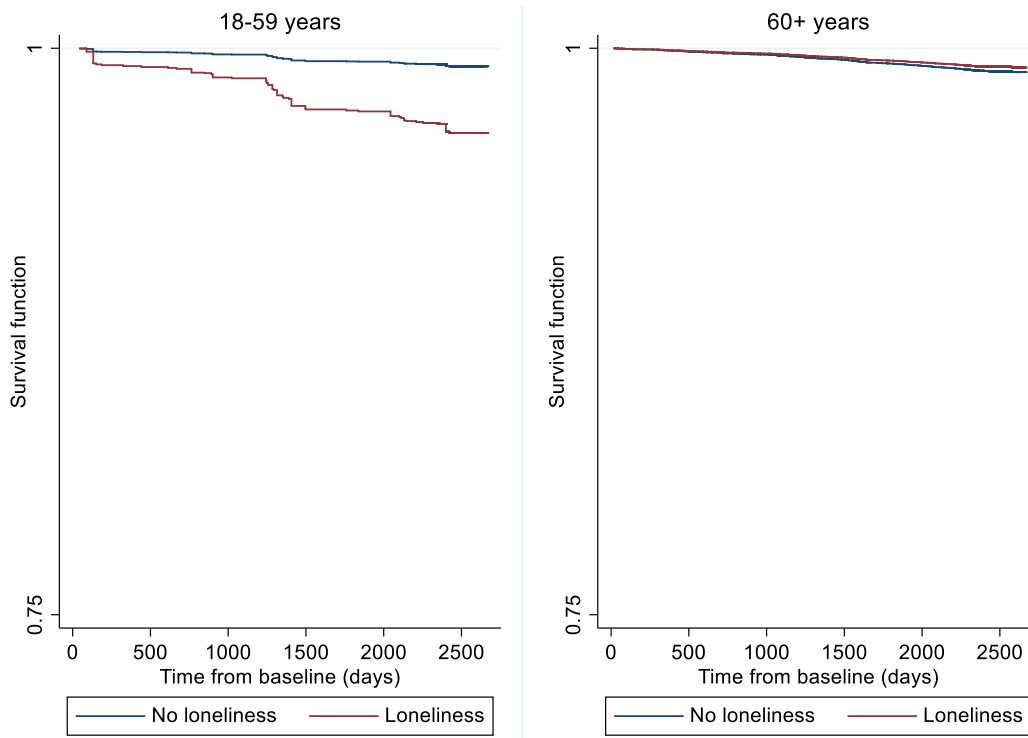
Figure 1. Survival function by age groups.
Notes. Survival functions were computed from the fully-adjusted Cox model. Covariates were fixed at their mean values. For the sake of clarity, loneliness has been categorised using a cut-off score of 6.

Author contributions

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475   Elvira Lara: Conceptualization; Elvira Lara, Darío Moreno-Agostino, Natalia Martín-

476   María, Marta Miret, Laura Alejandra Rico-Uribe, Beatriz Olaya: Data curation; Elvira

477   Lara: Formal analysis; Josep Maria Haro and José Luis Ayuso: Funding acquisition; All

478   authors: Methodology; José Luis Ayuso-Mateos: Supervision; Elvira Lara: Original draft;

479   All authors: Writing - review & editing.

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