Impacto de la soledad y las redes sociales sobre diferentes aspectos de la salud

Impact of loneliness and the social networks on different health aspects

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A mi familia por su gran apoyo e infinito amor

"La soledad y el sentimiento de no ser querido es la más terrible de las pobrezas."

Madre Teresa de Calcuta

"Cuando se enciende el amor, se apaga la soledad y el abandono. Con el amor termina la soledad y empieza el reconocimiento de la existencia."

Maru Maga,

El sótano de la golondrina y el príncipe feliz

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CONTENTS

1. RESUMEN

1.1. Resumen en español

Las relaciones sociales tienen características objetivas y subjetivas. La soledad es una característica subjetiva, mientras que el aislamiento social y los componentes de la red social son características objetivas. Ambas características, objetivas y subjetivas, tienen implicaciones en la salud, sin embargo, se necesita más investigación para entender las relaciones diferenciales de los componentes de las características sociales y los diferentes aspectos de la salud.

Esta tesis tiene como principal objetivo contribuir al conocimiento de la soledad, el aislamiento social y las redes sociales, evidenciando sus asociaciones con la salud auto-informada, el uso frecuente de los servicios de salud y la mortalidad. Este objetivo se alcanzó realizando tres estudios diferentes con objetivos específicos: a) evaluar la asociación diferencial que los componentes de la red social y la percepción subjetiva de soledad tienen con la salud y analizar si esta asociación difiere en distintos países; b) evaluar si el aislamiento social y la soledad están asociados prospectivamente con el uso de los servicios de salud, y si estas relaciones difieren en función del género; y c) analizar la asociación de la soledad con la mortalidad.

En relación con la metodología, el primer y el segundo estudio utilizan información del proyecto *COURAGE in Europe*. El primer estudio tiene un diseño transversal y el segundo un diseño longitudinal. La recogida de datos de línea base tuvo lugar en 2011-2012 en Finlandia, Polonia y España. El seguimiento se realizó en el 2014-2015 sólo en España. La metodología utilizada en el primer estudio fue la siguiente: un total de 10 800 adultos fueron entrevistados en Finlandia, Polonia y España; la soledad fue evaluada con la Escala de Soledad UCLA de 3 ítems. La red social de las personas se midió preguntando el número de miembros en la red, con qué

frecuencia tenían contacto con los miembros y si tenían una relación cercana. La asociación diferencial de la soledad y los componentes de la red social con la salud fue evaluada mediante modelos de regresión lineal jerárquicos, controlando por covariables relevantes. Para el segundo estudio, un total de 2528 adultos fueron re-entrevistados cara a cara a los tres años. El aislamiento social y la soledad se midieron con el Índice de Aislamiento Social y la escala de soledad de la UCLA de 3 ítems, respectivamente. Durante el seguimiento se obtuvo información sobre el uso de servicios de salud ambulatorios y hospitalizaciones. Se llevaron a cabo múltiples regresiones logísticas para analizar las asociaciones con el uso de servicios de salud. El tercer estudio fue un meta-análisis. Se buscaron en las bases de datos de Pubmed, PsycINFO, CINAHL y Scopus hasta junio 2016 los artículos publicados que estudiaban la relación entre la soledad y la mortalidad. Se extrajeron de cada artículo las características principales y los valores de tamaño del efecto de las relaciones. Adicionalmente, se llevó a cabo una evaluación de la calidad de los artículos incluidos. El meta-análisis se realizó primero con todos los artículos incluidos y, en segundo lugar, separando los tamaños del efecto por género mediante un modelo de efectos aleatorios.

Los resultados de los estudios son los siguientes: en el primer estudio se observó que la soledad tenía una asociación significativa con un peor estado de salud en Finlandia ($|\beta| = 0.25$), Polonia ($|\beta| = 0.16$) y en España ($|\beta| = 0.18$). En cuanto a los componentes de la red social, la frecuencia de contacto con los miembros de la red se asoció con un mejor estado de salud, mientras que la calidad del contacto y el tamaño de la red no estuvieron asociados. El segundo estudio mostró que la soledad (razón de posibilidades [OR]=1.12, 95% intervalo de confianza [CI]=1.02-1.24) y dos ítems del Índice de Aislamiento Social (no estar casado (razón de posibilidades [OR]=0.70, 95% intervalo de confianza [CI]=0.49-0.99) y tener menos de contacto mensual con otros

miembros de la familia (razón de posibilidades [OR]=2.08, 95% intervalo de confianza [CI]=1.12-3.85)) se asociaron con un uso frecuente de atención ambulatoria en las mujeres. Para los hombres, ni la soledad ni el aislamiento social fueron significativos para el uso de atención ambulatoria. Asimismo, se observó que ni el aislamiento social ni la soledad se asociaron con el uso de atención hospitalaria. Finalmente, en el tercer estudio se encontró que la soledad tiende a estar relacionada con la mortalidad (razón de posibilidades combinada [pooled HR] = 1.22; 95% CI = 1.10, 1.35, p = <0.001). Además, esta tendencia fue ligeramente superior en los hombres que en las mujeres (razón de posibilidades combinada [pooled HR] = 1.26; 95% CI = 1.07, 1.48, p = 0.005 para mujeres, y razón de posibilidades combinada [pooled HR]= 1.45; 95% CI = 1.17, 1.80, p = 0.001 para hombres).

Estos resultados llevan a concluir que la soledad, el aislamiento social y la red social están asociados con diferentes aspectos de la salud. La soledad, el aislamiento social y los componentes de la red social son un tema de importancia para la salud pública. Estos estudios también muestran que la soledad tiene una relación más fuerte con estos aspectos de la salud que el aislamiento social y la red social. Asimismo, esta tesis confirma los efectos adversos principalmente de la soledad. Es necesaria la distinción de las tres características sociales analizadas en esta tesis para tener una mejor comprensión y bordarlas adecuadamente.

1.2. Resumen en inglés

Social relationships have objective and subjective characteristics. Loneliness is a subjective characteristic whereas social isolation and the components of the social network are objective characteristics. Both characteristics, objective and subjective have health implications. However, more research is needed in order to understand the differential relationships of the components of the social aspects and different health aspects.

The main aim of this thesis is to contribute to the knowledge of loneliness, social isolation and social networks, providing evidence of their associations with self-reported health, frequent use of health services, and mortality. This aim will be reached by carrying out three different studies with specific aims: a) to assesses the differential association that the components of the social network and the subjective perception of loneliness have with health, and analyze whether this association is different across distinct countries; b) to evaluate whether social isolation and loneliness are prospectively associated with healthcare services use, and to assess whether these relationships differ by gender; and c) to analyze the association of loneliness with mortality.

In relation to the methodology, the first and the second studies use information from the project named *COURAGE in Europe*. The first study has a cross-sectional design whereas the second one has a longitudinal design. Baseline data collection took place in 2011-2012 in Finland, Poland and Spain. The follow-up was carried out in 2014-2015 only in Spain. The methodology used in the first study was the following: a total of 10800 adults were interviewed in Finland, Poland and Spain. Loneliness was assessed with the 3-item UCLA Loneliness Scale. Individuals' social networks were

measured by asking about the number of members in the network, how often they had contact with these members, and whether they had a close relationship. The differential association of loneliness and the components of the social network with health was assessed by means of hierarchical linear regression models, controlling for relevant covariates. For the second study, a total of 2528 adults were interviewed face-to-face three years later. Social isolation and loneliness were measured with the Social Isolation Index and the 3-item UCLA Loneliness Scale, respectively. Information about outpatient and inpatient care use at follow-up was obtained. Multiple logistic regressions were run to analyze the associations with healthcare use services. The third study was a meta-analysis. Pubmed, PsycINFO, CINAHL and Scopus databases were consulted through June 2016 for published articles that measured loneliness and mortality. The main characteristics and the effect size values of the relationships of each article were extracted. Moreover, an evaluation of the quality of the articles included was also carried out. The meta-analysis was performed firstly with all the included articles and secondly separating the effect sizes by gender, using a random effects model.

The results of the studies are the following: in the first study, it was observed that loneliness had a significant association with a worse health status in Finland ($|\beta| = 0.25$), Poland ($|\beta| = 0.16$) and in Spain ($|\beta| = 0.18$). Regarding the components of the social network, the frequency of the contact with the members of the network was associated with better health status whereas the quality of the contact and the size of the network were not associated. The second study showed that loneliness (odds ratio [OR]=1.12, 95% confidence interval [CI]=1.02-1.24) and two items from the Social Isolation Index (being unmarried (odds ratio [OR]=0.70, 95% confidence interval [CI]=0.49-0.99) and having less than monthly contact with other family members (odds

ratio [OR]=2.08, 95% confidence interval [CI]=1.12-3.85)) were associated with a frequent use of outpatient healthcare in women. Regarding men, neither loneliness nor social isolation were significantly associated with outpatient healthcare use. Moreover, social isolation and loneliness were not associated with inpatient care use. Finally, in the third study it was found that loneliness has a trend to be related with mortality (pooled HR = 1.22; 95% CI = 1.10, 1.35, p = <0.001). Furthermore, this trend was slightly higher in men than in women (pooled HR = 1.26; 95% CI = 1.07, 1.48, p = 0.005 for women and pooled HR = 1.45; 95% CI = 1.17, 1.80, p = 0.001 for men).

These results lead to conclude that loneliness, social isolation, and the social network are associated with different health aspects. Loneliness, social isolation and the components of the social network are important topics for public health. These studies also show that loneliness has a stronger relationship with these health aspects than social isolation and the social network. The distinction of the three social characteristics analyzed in this thesis is necessary in order to have a better understanding and properly manage them.

2. INTRODUCTION

2.1. Concepts and measures of objective and subjective social relationships characteristics

Humans are essentially social species, with a need for interacting, and forming relationships with other members of the species. Social relationships have objective and subjective characteristics (Cacioppo and Cacioppo, 2014), and it is necessary to define, measure, and analyze them independently without treating them as interchangeable.

Loneliness is considered as a subjective characteristic, and it is defined as the individual's subjective experience of the generalized lack of satisfying human relationships (Andersson, 1998). In this line, loneliness is related with social networks components, and these can predict (Hawkley et al., 2008) and spread (Cacioppo, Fowler, and Christakis, 2009) loneliness. According to the hypothesis formulated by Cacioppo et al. (2009), three social processes describe the placement of loneliness within a social network: a) *induction* explains that when a person feels lonely he or she may contribute to causing loneliness in other people of their network. Some feelings that a lonely person can experience are shyness, anxiety, anger, negative mood, hostility, social awkwardness, low self-esteem, or pessimism. Additionally, loneliness can influences the person´s personality (Cacioppo et al., 2006) what may lead to a trend of behaving in a less trusting and more hostile way with their network (Cacioppo and Patrick, 2008). This mode of acting may modify the relationship with others causing lower satisfaction, weakening, or losing the social tie, therefore contributing to the spread of loneliness to those with whom they interact; b) the *homophily* refers to the law of attraction proposed by Byrne (1971) which refers to the direct relationship of interpersonal attraction and the proportion of similar attitudes. Moreover, this law

mentions that this association between similarity and attraction not only refers to attitudes. The characteristics on which similarity acts transit from obvious characteristics (e.g. physical attractiveness) to less obvious ones (e.g. social perceptions), as the relationship advances and deepen. Even though the feelings of loneliness may be transitory, it is relevant to mention that these feelings have an effect on social cognition, emotion, and behavior to produce similarity-based social sorting; and c) *shared environment*, suggest that a group of individuals that share a similar environment could be exposed to jointly experiencing feelings of loneliness given that they are exposed to similar challenges and upheavals (e.g., widowhood, job loss, retirement, foreign students in their first year of university).

Although loneliness and social networks are related, it is relevant to highlight that they are different constructs; someone could feel lonely in a marriage or surrounded by a group of friends or in a party, while someone with a relatively solitary life or with few contacts may not feel lonely.

In order to adequately operationalize these constructs, different measures are required. Various instruments to measure loneliness have been developed such as the University of California Los Angeles (UCLA) Loneliness Scale, a 20-item scale with four response options (“I often feel this way”, “I sometimes feel this way”, “I rarely feel this way”, “I never feel this way”) (Russell, Peplau, and Ferguson, 1978); the De Jong Gierveld 11-item scale that differentiates and evaluates two components of loneliness: emotional and social (De Jong-Gierveld and Kamphuls, 1985); the Social Provisions Scale (SPS) (Cutrona and Russell, 1987) with 24-items distributed in the following subscales: attachment, reliable alliance, opportunity for nurturance, guidance, social integration, and reassurance of worth. The last three subscales were found to be significantly related to scores on the UCLA Loneliness Scale (Cutrona, 1982).

Moreover, another way of measuring this subjective characteristic is using select questions of previously created scales, such as the Center for Epidemiology Studies Depression Scale (CES-D) (Radloff, 1977), a 20-item questionnaire that evaluates depressive feelings and behaviors experienced during the previous week, which includes one item that asks whether the respondent felt lonely. This item is answered with a 4-point Likert scale that ranges from 0 (rarely or none of the time) to 3 (most or all of the time).

Some of the objective characteristics of social relationships include social networks and social support (Cacioppo and Cacioppo, 2014). When we refer to social support, we can distinguish between two forms: emotional support, defined as "someone being available to listen or offer sympathy during times of crisis or hardship, or someone available to give advice", and instrumental support, defined as "someone available to offer help with issues that require physical effort or financial aid" (Santini, Koyanagi, Tyrovolas, Mason, and Haro, 2015). On the other hand, when we talk about social networks, we are referring to a web of social relationships that surrounds a person, comprised of the contacts and the nature of the connections (Smith and Christakis, 2008). In general terms, this characteristic ignores the individual´s perception and quantifies the connections between the members of the network (Cacioppo et al., 2009). In the social network, we can distinguish three components: 1) the size of the network, which refers to the number of contacts of the social network; 2) the frequency of contact with the members of the network, which could be physical contact, writing contact, telephone calls, or virtual communication; and 3) the quality of the network, which refers to how close the person perceives their relationships with the members of the social network.

The objective characteristics mentioned above are evaluated through different questionnaires. One of the most frequently used scale to evaluate social support is the 3-item OSLO Social Support Scale (Brevik and Dalgard, 1996). This tool allows for assessing the number of close friends with the question: “How many people are so close to you that you can count on them if you have serious problems?”; perceived concern is assessed with the question: “How much concern do people show in what you are doing?”; and the practical help from others is assessed by asking: “How easy can you get help from neighbors if you should need it?”. The total sum score ranges from 3 to 12. Another questionnaire that assesses social support is the Interpersonal Support Evaluation List-12 item. This questionnaire has 3 subscales that measure different dimensions of perceived social support: appraisal support, belonging support, and tangible support. Each dimension is measured with 4 items on a 4-point response scale ranging from “definitely true” to “definitely false” (Cohen, Mermelstein, Kamarck, and Hoberman, 1985). The Berlin Social-Support Scales (BSSS) also evaluates social support, with 6 subscales: perceived support, need for support, support seeking, protective buffering, actually provided and received support. All these subscales measure both cognitive and behavioral aspects of social support. The answering format is with a four-point scale: strongly disagree (1), somewhat disagree (2), somewhat agree (3) and strongly agree (4) (Schwarzer and Schulz, 2003). In relation to the social networks, a highly used instrument is the Berkman-Syme Social Network Index, which considers not only the number of social ties but also their relative importance. This is a self-report questionnaire for use in adults, and mainly assesses 1) the number of social contacts that the person has, 2) their relative importance, also known as closeness with the members of the social network, and 3) the frequency of contact with the person´s current social network (Berkman and Syme, 1979).

In this line, another relevant objective characteristic, which is highly associated (Hawkley et al., 2008; Matthews et al., 2016) and sometimes confused with loneliness (Miller, 2011), is the social isolation. This characteristic is an "objective and quantifiable reflection of reduced social network size and paucity of social contact" (Steptoe, Shankar, Demakakos, and Wardle, 2013). Social isolation is frequently measured with a index developed by Steptoe et al. (2013) that assigns one point if the respondent is unmarried/not cohabiting; a second point if he or she has less than monthly contact (including face-to-face, telephone, or written/e-mail contact) with children or does not have children; a third point if he or she has less than monthly contact with other family members or does not have other family members; a fourth point if he or she had less than monthly contact with friends or does not have friends; and fifth point if he or she does not participate in organizations such as social clubs or residents groups, religious groups, or committees. The score ranges from 0 to 5 with higher scores indicating greater social isolation.

2.2. Prevalence, age and gender differences, and cultural aspects

According to Linehan et al. (2014) loneliness and social isolation have become a relevant issue for public health. A recent article that focuses on the prevalence of loneliness in European countries showed that the percentage of lonely people in Western and Northern countries is 10% whereas in Eastern countries is 55% (Hansen and Slagsvold, 2016). The age group with the highest prevalence of loneliness is older adults (Dahlberg, Andersson, McKee, and Lennartsson, 2015; Pinquart and Sorensen,

2001), a group that is becoming increasingly larger. It is expected that in 2060, the population of older adults will be nearly the same size as the young (Part, 2014). A study carried out by Saito et al. (2010) found that the prevalence of socially isolated elderly is around 24%. According to a systematic review of Nicholson (2012), elderly people are more vulnerable to feeling lonely or to being isolated due to several reasons: a) they are more prone than younger people to having health problems that might make it more difficult to interact or develop new social relationships (e.g., poor vision, hearing loss, urinary incontinence, or sleep problems); b) neuropsychological aspects such as cognitive decline may also decrease social engagement; c) the retirement process can be a stressful event, and it is related with a decrease in social network contact, thus leading to social isolation; d) in this age group it is common to experience work and family changes that might be related to loneliness and social isolation, (e.g., loss of a family member or neighbor, widowhood, empty nest syndrome, loss of contact with colleagues and friends from work); and e) environmental changes such as transformations or variations in the neighborhoods: if the person used to visit their friends, shops, or frequent places to socialize, and suddenly these disappear it may contribute to reducing the network of the person. Another environmental change is the safety aspect: an increase of insecurity may limit the persons to socialize outdoors. In addition, the reorganization of the household size may influence loneliness and social isolation if it means that the elderly person is living alone.

In addition, gender differences have been found in relation to loneliness, social isolation and social networks. Cacioppo et al. (2009) suggested that loneliness spreads more easily in women than in men given the characteristics of their social ties. The way of building social networks is different in both gender groups; for example, men experience smaller social networks (Pinquart and Sorensen, 2001) and less intimate

relationships (Borys and Perlman, 1985). Moreover, it is necessary to take into consideration gender when trying to understand loneliness, given that women have a higher risk of loneliness than men (Dahlberg et al., 2015). It is crucial to analyze both groups independently because the risk factors that could be found for the total population could not be the same for a specific gender group. An example of a life situation that varies between genders is that of life expectancy, which is longer in women than men (World Health Organization, 2016). This can be significantly related to loneliness, social networks, and social isolation, since widowhood as well as living alone, occur earlier and are more common in women than in men (Aartsen and Jylha, 2011). Additionally, it is culturally less acceptable for men to express their emotions than it is for women (Tijhuis, De Jong-Gierveld, Feskens, and Kromhout, 1999).

Cultural aspects are related with loneliness, social isolation, and social networks as well. Earlier studies analyzing loneliness (Dykstra, 2009; Fokkema, De Jong Gierveld, and Dykstra, 2012) and social networks (Litwin and Stoeckel, 2013) found differences across countries. Different studies have reported that people from northern European countries tend to feel less lonely than people from southern and central European countries (Fokkema et al., 2012; Sundström, Fransson, Malmberg, and Davey, 2009). In regard to social networks, Dykstra (2009) found that the relationships in northern European countries, and southern and central European countries are different: the former are individualistic countries whereas the latter, according to Reher (1998), usually have relatively strong ties, and they have frequent contact with their family. For example: the process of emancipation from the parents' house is sometimes delayed until after marriage, grandparents often live near their sons and daughters to give support, and the care of the elderly is mainly carried out by the members of the family.

2.3. Health implications of different social characteristics

The conceptualization and measurements of the characteristics of the social relationships previously mentioned emphasize specific aspects of the connections between individuals. In this line, previous evidence has shown that social relationships are relevant to mental and physical health (Cacioppo and Cacioppo, 2014).

In relation to loneliness, Cacioppo and Cacioppo (2014) explain that experiencing these feelings in the short-term could be part of an adaptation and evolutionary behavior, e.g. when a student leaves his family to go to university or when a businessman takes a job in a new town (Miller, 2011). However, if these feelings become a chronic condition they could have biological, cognitive, and social consequences. Lonely individuals have poorer health than non-lonely individuals (Cacioppo et al., 2002; Cacioppo, Hawkley, and Thisted, 2010). Previous research has found that people who suffer from lonely feelings have lower cardiovascular contractility, heart rate, cardiac output (Cacioppo et al., 2002), and alterations in the immunological system (Pressman et al., 2005). Also, these feelings are related to obesity (Lauder, Mummery, Jones, and Caperchione, 2006), alcoholism (Akerlind and Hornquist, 1992), Alzheimer's disease (Wilson et al., 2007), and sleep problems, mainly poor sleep efficiency and quality (Cacioppo et al., 2002; Pressman et al., 2005). Moreover, loneliness has been associated with depression. A 5-year longitudinal study carried out with 229 participants aged 50-68 years old showed that loneliness was related to depressive symptomatology, and this temporal relationship was not attributable to socio-demographic variables, dispositional negativity, stress, or social support (Cacioppo et al., 2010). Furthermore, results of a study carried out in England

and Wales by Matthews et al. (2016) showed a significant association of loneliness with depression during young adulthood. Feeling lonely is also related to suicidality. According to the study by Schinka, Van Dulmen, Bossarte, and Swahn (2012), loneliness is concurrently associated with both suicidal ideation and suicidal behavior. The demographic characteristics measured in the study did not influence this relationship.

On the other hand, if we focus on the objective characteristics, mainly on social networks, we can find extensive literature regarding its significant relationship with physical and mental health (Smith and Christakis, 2008). It has been found that the quantity and quality of social relationships (Ryan and Willits, 2007; Szreter and Woolcock, 2004), as well as the frequency of contact (Fernández–Ballesteros, 2002), may have a significant impact on health. In this line, the literature shows that social networks play a protective role against depression (Santini et al., 2015), and an extensive social network protects against dementia (Berkman, Glass, Brissette, and Seeman, 2000; Fratiglioni, Wang, Ericsson, Maytan, and Winblad, 2000). Furthermore, the study of Cohen, Doyle, Skoner, Rabin, and Gwaltney (1997) suggests that people with more types of social ties had greater resistance to respiratory diseases than those with less social ties. According to Ramlagan, Peltzer, and Phaswana-Mafuya (2013), married people or those living with their romantic partner, those with high levels of trust and solidarity, as well as those with medium-to-high psychological resources, reported better health. Litwin and Landau (2000) found that social networks and social support are related, given that the first one predicts the availability of social support.

Socially isolated persons also have a higher risk of experiencing negative health outcomes such as cardiovascular diseases (Steptoe et al., 2013). In a study by Coyle and Dugan (2012), carried out with a sample of 11,825 older adults, it was found that social

isolation and loneliness have independent pathways of association with health; the first one is related with higher odds of self-reporting health as fair or poor, whereas the second one is more strongly associated with mental health. Also, this study concluded that measures that do not distinguish between social isolation and loneliness might not detect their correct impact on physical and mental health. Nevertheless, there are studies that, contrary to the previous finding, observed a significant correlation between social isolation and mental health, mainly with depressive symptoms (Matthews et al., 2016). A longitudinal study that followed up 1,037 children since they were born until the age of 26 years showed that being socially isolated during childhood was a significant risk factor of poor health in adulthood (Caspi, Harrington, Moffitt, Milne, and Poulton, 2006). This longitudinal relationship was independent of other childhood risk factors for poor adult health such as low childhood socioeconomic status, low childhood intelligence quotient (IQ), and childhood overweight.

Although the previous literature has been studying these aspects, there is a need to analyze them simultaneously to see the differential effects of each construct and its components on health, mortality and the use of healthcare services. Furthermore, it may be that these constructs co-occur in parallel even though they are thought to be independent constructs (Matthews et al., 2016).

2.4. Health services implications of different social characteristics

Given that social relations have health implications, it follows that these constructs may also have implications on the use of health services.

Previous studies show that both social isolation and loneliness contribute to the frequent use of healthcare services. Ellaway, Wood, and Macintyre (1999) found that lonely people have a higher number of general physician visits than non-lonely people. Similar results were obtained in the study of Cheng (1992), even after controlling for health conditions, which are highly related to the use of health services. In addition, studies carried out with elderly people suggest that loneliness is associated with a high number of visits to the physician (Cheng, 1992; Gerst-Emerson and Jayawardhana, 2015).

In relation to social isolation, Bellido-Zanin, Pérez-San-Gregorio, Martín-Rodríguez, and Vázquez-Morejón (2015) found that in patients with severe mental disorders, this construct predicts the use of mental health services. Moreover, a poor social network is related to frequent hospital readmissions (Mistry et al., 2001; Rodríguez-Artalejo et al., 2006). On the other hand, Iliffe et al. (2007) found that for first admissions and primary care use or outpatients appointments, social isolation was not significant.

2.5. The association of social characteristics with mortality

Some studies have also reported that lonely individuals show an increased risk of all-cause mortality (Luo, Hawkley, Waite, and Cacioppo, 2012; Tilvis, Laitala, Routasalo, and Pitkala, 2011), and early mortality (Drageset, Eide, Kirkevold, and Ranhoff, 2013; Perissinotto, Stijacic Cenzer, and Covinsky, 2012). In relation to social isolation and the lack of social networks, a study with a 10 year follow-up period showed that men with fewer social ties had a higher risk of all-cause mortality than

those with more ties (Eng, Rimm, Fitzmaurice, and Kawachi, 2002). Additionally, Udell et al. (2012) suggested that being isolated is associated with a significantly higher risk of cardiovascular mortality.

The studies that analyzed social isolation and loneliness together have also found significant results. A recent meta-analysis that studied both constructs as risk factors of mortality showed that social isolation increased the likelihood of dying by 29%, and loneliness increased it by 26%. The authors also concluded that the impact of both factors on mortality is comparable with other well-established risk factors for mortality (Holt-Lunstad, Smith, Baker, Harris, and Stephenson, 2015). Besides, in the study of Steptoe et al. (2013) carried out with English people aged 52 and older, it was found that social isolation and loneliness were longitudinally related with mortality. However, when the authors adjusted the analyses to control for demographic characteristics and baseline health, social isolation remained significant but loneliness did not.

2.6. Gaps in the literature

Previous authors have suggested that there is a need for more research that differentiates between the subjective and objective characteristics of social relationships, and that disentangles their components (Coyle and Dugan, 2012; Hawkley and Cacioppo, 2010). Furthermore, it is necessary to analyze these constructs individually, as well as simultaneously, to observe their differential impact on health, mortality and the use of healthcare services. Finally, additional studies that consider

cultural, gender and age aspects are needed given that the social characteristics of these groups are distinct.

The present thesis was born as a result of the bibliographic revision and the findings of above-mentioned gaps in the literature. The work includes one published article and two articles currently under review that analyze the impact of loneliness, social isolation and social networks on health, mortality and the use of healthcare services. The first article is a cross-sectional study carried out in three countries that focuses on loneliness, social relationships and health. The second study analyzes the prospective relationship of social isolation and loneliness with the use of healthcare services. The third study is a meta-analysis of gender differences in the association of loneliness with mortality. In the chapter "Studies included in the thesis" each study is described in detail with its methodology, results and discussion. In the chapter "Results", the main findings of each study are summarized.

2.7. Contributions of the author

This thesis is based on one article published in the scientific journal PLOS ONE, a second study under the second review in the journal Health Services Research, and a third study under the first review also in the journal PLOS ONE. The author of this thesis is the leading (first) author of the three papers. Moreover, the author has participated in the development of the second wave of the *COURAGE in Europe – Edad con Salud Project*, used in two of the studies. The main activities in which the author participated were in the teleconferences regarding coordination and project

management, in the revision and restructuration of the questionnaire, in the training of the interviewers that carried out the fieldwork, and in the data cleaning. The contribution in the *COURAGE in Europe - Edad con Salud Project*, resulted in collaborations as co-author in other published articles that are listed in the Annexes.

Furthermore, during the four years spent as a doctoral student, the author participated in the dissemination of the results in two international congresses: 1) XVI World Congress of Psychiatry "Focusing on access, quality and humane care", and 2) Eleventh International Conference of the European Network for Mental Health Service Evaluation (ENMESH).

In addition, the doctoral student had the opportunity to carry out two internships in international institutions (World Health Organization, and the Ludwig-Maximilians-Universität München) for research training and improvement of research skills to develop the thesis. Moreover, during the period of the fellowship, she attended different national and international courses in order to improve her research and teaching aptitudes.

Finally, the author provided support in different meetings carried out by the Psychiatry Department of the Universidad Autónoma de Madrid and the World Health Organization Collaborating Center for Mental Health Services Research and Training. During this time, she also carried out teaching collaborations in the Medical Psychology and Psychiatry courses.

3. OBJETIVOS E HIPÓTESIS

3.1. Objetivos

El principal objetivo de la presente tesis doctoral es contribuir al conocimiento de la soledad, el aislamiento social y las redes sociales, proporcionando evidencia de su asociación con la salud auto-informada, el uso frecuente de servicios de salud y la mortalidad.

Los objetivos específicos en relación con la asociación con la salud auto-informada son:

I. Desgranar la asociación diferencial de los diferentes componentes de las redes sociales (la calidad y el tamaño de la red social, y la frecuencia del contacto con los miembros de la red) y la percepción subjetiva de la soledad con la salud.

II. Analizar el poder explicativo adicional de cada uno de los elementos de las redes sociales (la calidad y el tamaño de la red social, y la frecuencia del contacto con los miembros de la red) y la soledad en su asociación con el estado de salud.

III. Examinar si la relación de los diferentes componentes de las redes sociales (la calidad y el tamaño de la red social, y la frecuencia del contacto con los miembros de la red) y la percepción subjetiva de la soledad con la salud es diferente entre tres países europeos (España, Finlandia, y Polonia).

El objetivo específico en relación con la asociación con el uso frecuente de servicios de salud es:

IV. Evaluar si la soledad y los diferentes componentes del aislamiento social están asociados con el uso frecuente de servicios ambulatorios y hospitalizaciones, y examinar si esta asociación difiere por género.

El objetivo específico en relación con la asociación con la mortalidad es:

V. Determinar si la soledad está asociada con la mortalidad, y saber si esta asociación es similar en hombres y en mujeres.

3.2. Hipótesis

Las hipótesis específicas en relación con la asociación con la salud auto-informada son:

I. Los componentes de la red social y la soledad estarán asociados con el estado de salud.

II. La soledad estará más asociada con la salud que el tamaño de la red social, la frecuencia de contacto con los miembros de la red y la calidad de la red social.

III. La asociación entre las variables previamente mencionadas y el estado de salud será diferente entre los países, dado sus diferentes sistemas de

protección social, situación económica, estructura de las redes sociales y lazos familiares.

La hipótesis específica en relación con la asociación con el uso frecuente de servicios de salud es:

IV. El aislamiento social y la soledad estarán asociados con el uso frecuente de servicios ambulatorios y hospitalizaciones. La relación entre las variables mencionadas previamente y el uso de servicios de salud será significativa en mujeres y en hombres.

La hipótesis específica en relación con la asociación con la mortalidad es:

V. La soledad estará asociada con la mortalidad y esta asociación será similar en ambos géneros.

4. METODOLOGÍA

La metodología empleada en cada uno de los tres estudios que conforman esta tesis doctoral, está descrita detalladamente en el siguiente capítulo titulado “Studies included in the thesis”.

5. STUDIES INCLUDED IN THE THESIS

This chapter includes the three studies that construct this thesis. Each study is described in detail, and they are presented exactly as they were submitted to each journal.

5.1. Loneliness, social networks, and health: A cross-sectional study in three countries

† **Title:** Loneliness, social networks, and health: A cross-sectional study in three countries

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Abstract

Objective: It is widely recognized that social networks and loneliness have effects on health. The present study assesses the differential association that the components of the social network and the subjective perception of loneliness have with health, and analyzes whether this association is different across different countries.

Methods: A total of 10 800 adults were interviewed in Finland, Poland and Spain. Loneliness was assessed by means of the 3-item UCLA Loneliness Scale. Individuals' social networks were measured by asking about the number of members in the network, how often they had contacts with these members, and whether they had a close relationship. The differential association of loneliness and the components of the social network with health was assessed by means of hierarchical linear regression models, controlling for relevant covariates.

Results: In all three countries, loneliness was the variable most strongly correlated with health after controlling for depression, age, and other covariates. Loneliness contributed more strongly to health than any component of the social network. The relationship between loneliness and health was stronger in Finland ($|\beta| = 0.25$) than in Poland ($|\beta| = 0.16$) and Spain ($|\beta| = 0.18$). Frequency of contact was the only component of the social network that was moderately correlated with health.

Conclusions: Loneliness has a stronger association with health than the components of the social network. This association is similar in three different European countries with different socio-economic and health characteristics and welfare systems. The importance of evaluating and screening feelings of loneliness in individuals with health problems should be taken into account. Further studies are needed in order to be able to confirm the associations found in the present study and infer causality.

Keywords: social network, loneliness, health status, hierarchical linear regression models.

Introduction

The association between social relationships and health is well documented and has been of interest to the scientific community for many years (1-3). Much of the earlier literature used different concepts interchangeably, such as feeling lonely, living in a single household, having few social contacts or a small social network, or not having people to trust; however, recent studies have made important advances by moving beyond simple indicators related to marital status or living arrangements, to analyze different dimensions and dynamics of social networks (4, 5) and separating these effects from those of feelings of loneliness (6).

There is considerable evidence that the nature and extent of an individual's social network, such as quantity and quality of social relationships (7, 8) and frequency of contact (9), can have a significant impact on health. An extensive social network has been shown to be a protective factor against dementia (2, 4). Furthermore, older people who are married or cohabiting and those with high levels of trust and solidarity, as well as those with medium-to-high psychological resources, all experience better self-rated health (10). Social networks and social support are related, since they are part of the same construct (11); however, they focus on different aspects and should be evaluated separately. Litwin and Landau (12) found that the significance of the social network predicts the availability of social support. A systematic review carried out by Santini, et al. (11) investigated the association between social relationships and depression, and found that social networks play a protective role against depression, just as social support does.

On the other hand, loneliness may have deleterious effects on health (13, 14). Lonely individuals have lower cardiovascular contractility, heart rate, and cardiac output than non-lonely individuals (13); they are also more likely to present alterations in the immunological system (15) and obesity (16). Loneliness is also associated with poorer sleep efficiency and quality (13, 15), depressive symptomatology (14), alcoholism (17), Alzheimer's disease (18),

and suicidal ideation and behavior (19). Furthermore, some studies report that lonely individuals also show an increased risk of all-cause mortality (20, 21).

Although previous evidence shows that social networks and loneliness have effects on health (22), there is still a need to know whether the relationship between the subjective perception of loneliness and health is different from the relationship between each component of the social network and health, after controlling for potential confounders, and to analyze with identical methods whether these relationships are different across countries with different population, health, and socio-economic characteristics and family structures. International studies have clearly documented the difference in health across countries with different social welfare systems (23). Earlier studies analyzing loneliness (24, 25) and social networks (26) found differences across countries. Moreover, differences across generations have been documented in previous studies. Jylha (27) found that age is related to negative life changes that increase loneliness and weaken social integration, whereas Carstensen (28) suggested that although social networks grow smaller with advancing age, they also grow more satisfying.

In addition, more research is needed to better understand the differences between the concepts by analyzing separately loneliness and the number of contacts with members of the network, since these are two different concepts: loneliness is a subjective feeling, and the number of contacts is an objective aspect (6, 29). Previous studies found that the subjective experience of loneliness is more harmful to health than the actual number of the social contacts that a person has (29). A longitudinal study found that loneliness predicts changes in depressive symptoms, and the association between these variables is not attributable to objective social isolation, emotional closeness in relationships or social support (14). Although social networks have been well documented and loneliness is now being increasingly studied, to our knowledge few studies have been carried out that analyze both

variables at the same time (loneliness and size of the network), much less that disentangle and analyze separately the other components of the social network: frequency and quality of contact.

The present study aims to: a) disentangle the differential associations of health with the different components of the social network (size and quality of the network, and frequency of contact with members of the network) and the subjective perception of loneliness; b) analyze the additional explanatory power of each of the elements in their association with health status; and c) examine whether this association differs across countries.

The hypotheses postulated are: a) the components of the social network and the subjective perception of loneliness will be associated with health status; b) loneliness will be more associated with health than the size, frequency and quality of social networks; c) the association between the aforesaid variables and health status will be different across the countries considered in this study, due to their different social protection systems, economic situations, social network structures, and family ties.

Method

Design

The Collaborative Research on Ageing in Europe (COURAGE in Europe) project (http://courageproject.eu/) (30) is a European Union-funded, cross-sectional household survey of a probabilistic sample representative of the adult population aged 18+ years, in three European countries (Finland, Poland and Spain). Nationally representative samples were obtained for each of the three countries according to the procedure described below. These countries were selected to give a broad representation of different European regions,

representing Northern, Eastern and Southern Europe according to the classification of the United Nations (31), and different demographic, cultural, socio-economic and health characteristics, as well as different social welfare systems (23).

Sample and procedure

Participants were interviewed face-to-face in their own homes, with Computer-Assisted Personal Interviewing. The surveys were conducted between April 2011 and May 2012. The COURAGE survey questionnaire was translated from English into Finnish, Polish, and Spanish following the World Health Organization translation guidelines for assessment instruments. These include a forward translation, a targeted back-translation, review by a bilingual expert group, and a detailed translation report. The questionnaire used in the present study is shown in Appendix S1. Quality assurance procedures were implemented during fieldwork (32).

A multistage clustered design was used to obtain nationally representative samples in each country. In Poland and Spain, a stratified multistage random sampling method was used and strata were created according to the geographical administrative regions and number of people living in the geographical area. Age strata were used to select households according to the age structure of the population. The respondents were randomly selected among inhabitants of a household from a certain age group. In Finland, the design was a stratified two-stage cluster sampling design, and strata were created based on the largest towns and university hospital regions. A systematic sampling of people was conducted so that the sample size in each stratum was proportional to the corresponding population base. Although the samples were representative of the population of the three countries, the group of people older than 80 years was overrepresented in the sampling in order to avoid having a small sample size of the oldest old.

A total of 10 800 individuals participated in the survey: 1976 from Finland, 4071 from Poland, and 4753 from Spain. The individual response rate was 53.4% for Finland, 66.5% for Poland, and 69.9% for Spain. The present study was approved by the ethical committee of Neurological Institute Carlo Besta, Milan, Italy, project coordinator; the Ethics Review Committee, National Public Health Institute, Helsinki, Finland; the Bioethical Committee, Jagiellonian University, Krakow, Poland; Ethics Review Committee, Parc Sanitari Sant Joan de Déu, Barcelona, Spain; and Ethics Review Committee, La Princesa University Hospital, Madrid, Spain. Written informed consent from each participant was also obtained.

Measures

Loneliness was assessed by means of the 3-item UCLA Loneliness Scale (33). This scale comprises the following items: *How often do you feel that you lack companionship?*, *How often do you feel left out?* and *How often do you feel isolated from others?*, which are assessed on a 3-point scale (1 = hardly ever; 2 = some of the time; 3 = often). The UCLA Loneliness Scale has shown satisfactory reliability and both concurrent and discriminant validity (33). The scale showed acceptable internal reliability in the present study (Cronbach's alpha = 0.84; mean inter-item correlation = 0.65). The scores for each item were added up to produce a loneliness score ranging from 3 to 9, with higher scores indicating higher loneliness levels.

A detailed description of the individual's social network was obtained. It included the following components: 1) size of the network; 2) frequency of contact with members of the network; and 3) quality of the network. The three components of the social network considered are based on the structural dimension of the Berkman-Syme Social Network Index (34), which measures the number of social ties, closeness with members of the network, and frequency of contact. The size of the network was assessed by asking the participant about

the number of people in the network("*Please state the number of people [in total] who are so close to you at the present time that you: can talk to them about personal affairs, can get help from them in everyday matters, and/or enjoy spending your leisure time with them [please consider family members, friends, colleagues, etc.]"*). The variables frequency of contact with members of the network (also known as intensity of the network) and quality of the network were assessed with an index ranging from 0 to 8, asking the person if they had had contacts with the members of the network at least once per month in the previous 12 months and whether they had a close relationship with them. One point was assigned for each of the eight types of the relationship: spouse or partner, parents, children, grandchildren, other relatives, co-workers, friends, and neighbors. This scoring method is based on the Social Network Index proposed by Cohen (35), which assesses participation in several types of relationships.

Health status was assessed with a multi-domain health state measurement that considers that health is more than the absence of disease or injury; it also takes into account the ability to carry out physical and mental actions, and tasks (36). This measure was developed after the World Health Organization (WHO) argued, "functioning and functioning domains constitute the operationalization that best captures our intuitive notion of health" (37). This health measure has been previously used in the 70 countries considered in the World Health Survey and in the WHO Study on Global AGEing and adult health, to compare the health of the population around the world. It is a set of self-reported health-related questions that were grouped into eight health domains: vision, mobility, self-care, cognition, interpersonal activities, pain and discomfort, sleep and energy, and affect (36). For each question, responses were recorded on a 5-point scale ranging from no difficulty/problem to extreme difficulty/inability. An overall health score from these health-related questions was

obtained using a Rasch partial credit model (38). The overall health score ranged from 0 to 100, where 0 represents the worst health and 100 represents the best health.

The presence of a depressive episode during the previous 12 months was assessed with a set of questions based on the World Mental Health Survey version of the Composite International Diagnostic Interview (39). Individuals were considered to have had a depressive episode if they had been diagnosed with depression and had been taking medication or receiving some other treatment (e.g. psychotherapy) during the previous 12 months, or if they reported the presence of the core symptoms of the condition during the previous 12 months, according to ICD-10 Diagnostic Criteria for Research (40).

Participants were also asked to provide socio-demographic information: age, gender, years of education, residential setting (rural, urban), household composition (living in a single household, a dual household, or a household with three or more people), and household income. Marital status was dichotomized as either married or in a partnership, or not married or in a partnership (including single, divorced, widowed, or not living with a partner), similarly to other studies that also analyzed loneliness (41, 42). A 5-level ordinal variable for household income was obtained, representing the quintile of household income according to the country. This variable was then dichotomized, with belonging to the first or the second quintile of household income considered as the reference category.

Statistical analysis

All data were weighted to account for the sampling design in each country and to generalize the study sample to the reference population. Normalized weights for each age group (18-49 and 50+ years) were used. Post-stratification corrections were made to the weights to adjust for the population distribution obtained from the national census from each country, and for non-response (43). Rates and means were calculated using the direct method of age standardization to the European standard population (44). Robust standard errors were

estimated using the Taylor series linearization method (45) to adjust for the effects of weighting and clustering.

Analysis of variance (ANOVA) tests and χ^2 tests were used to assess differences across countries in socio-demographic characteristics, components of the social network, and loneliness. The mean estimates on the components of the social network, loneliness, and health status were obtained separately for each age group (18-49 and 50+ years) in order to take into account the specific sampling weights considered for each group. Differences across countries were assessed for each age group and for the overall population. Cramer's *V* (χ^2 test), Cohen's *f* (ANOVA) and Hedges' *g* (pairwise comparisons) were reported as effect size measures in case of significant differences at the 95% confidence level. Cohen's guidelines (46) were used as standard to evaluate the magnitude of the effect size. Cramer's *V* values of 0.10, 0.30, and 0.50 constitute small, medium, and large effect sizes; whereas these values are 0.10, 0.25, and 0.40, respectively, for Cohen's *f*. Hedges' *g* values of .20, .50, and .80, constitute small, medium, and large effect sizes, respectively.

Pearson correlation coefficients assessed the relationships between the components of the social network among themselves, and with loneliness. In order to look at the independent effect of social networks (in terms of size of the network, frequency of contact with members of the network, and quality of the network) and loneliness on health status, a hierarchical linear regression model was conducted in each of the three countries considered in the present study. A first block comprising socio-demographic variables and the presence of a depressive episode was included to account for their effect. Depression was added as a potential confounder identified in the literature, since it has long been recognized that loneliness and depressive symptoms are strong correlates (14, 47-51). Moreover, Cacioppo et al. (48) concluded that loneliness and depressive symptoms could act in a synergistic way to reduce health. Then, the three components of the social network and the loneliness score were

introduced in two different blocks to assess their differential association with health. The increase in the proportion of variance explained in each block (increase in the adjusted R^2) was tested at each step by means of the difference in the likelihood ratio chi-square for each model, which tested the null hypothesis that each additional set of independent variables contributed nothing beyond the set(s) of variables entered in the model(s) at earlier steps. The Ordinary Least Squares (OLS) estimator, which trades robustness for some improvement in efficiency (52) and has been shown to yield the best fit of data (53), was used for each model. Beta coefficients were reported, and can be interpreted as change in the outcome (in standard deviations) per standard deviation change in the predictors; they were used to assess which variables had the highest association with the outcome variable.

A multiple linear regression model was estimated over the pooled sample, including only the variables that were found significant in at least one of the previous models conducted for each country. Dummy variables for countries were included in this model; moreover, interaction terms between countries and the variables related with social networks and loneliness were added to account for country differences with regard to the association of social networks and loneliness with health. Interaction terms between age (considered as a continuous variable) and loneliness, and between gender and loneliness, were also included.

Finally, gender differences in loneliness scores were assessed in each country by means of unpaired *t*-tests, reporting Hedges' *g* as effect size measures. Loneliness scores for different age groups were also analyzed by country.

Data analysis was performed incorporating the sample weights and using Stata version 11.0. Stata's survey command (svy), which fits statistical models for complex survey data, was used. Confidence intervals (CI) for hypothesis tests were constructed at the 95% confidence level.

Results

The final sample comprised 10 047 participants and was obtained after excluding the participants who did not answer the questions about their social network or their perception of loneliness. Even though the excluded sample (n = 753) did not differ by gender (57.4% women in the final sample vs. 56.6% women in the excluded sample, p = 0.67) or percentage of people living in a rural setting (26.7% vs. 25.0%, p = 0.25), the percentage of people married or in a partnership (59.1% vs. 53.0%, p = 0.002, Cramer's V = 0.03) and the mean age (58.35 ± 16.77 in the final sample vs. 70.00 ± 17.41 in the excluded sample, p < 0.001, Hedges' g = 0.69) were significantly different, albeit associated with very small effect sizes. Table 1 shows the socio-demographic characteristics of the final sample separately by each country. In general terms, while the differences found in socio-demographics across countries were significant, they were also associated with a small effect size.

Table 1. Socio-demographic characteristics of the final sample, by country.

	Finland	**Poland**	**Spain**	**Effect size**
Number of participants (*n*)	1821	3851	4375	-
Gender (%)				0.05
Female	56.95	60.17	55.09	
Male	43.05	39.83	44.91	
Age, Mean (SD)	58.21(16.03)	56.96(17.94)	59.63(15.89)	0.07
Current marital status (%)				0.05
Not married	36.96	44.12	39.73	
Married or in partnership	63.04	55.88	60.27	
Residential setting (%)				0.30
Rural	22.02	43.34	13.94	
Urban	77.98	56.66	86.06	
Years of education, Mean (SD)	12.35 (4.25)	11.73 (3.82)	10.94 (6.28)	0.10
Household composition (%)				0.10
Living in a single household	29.21	25.58	19.45	
Living in a dual household	47.39	37.86	38.22	
Living in a household with three or more people	23.39	36.56	42.33	

Effect size: Cramer's V for χ^2 tests (categorical variables) and Cohen's f for ANOVA tests (quantitative variables). Effect size was reported for all the differences that were found to be significant at the 95% confidence level.

As shown in Table 2, the lowest score on loneliness was found in Finland. The size of the network was greater in Finland and Spain, whereas the quality of the network was better in Poland than in Finland and Spain. Significant differences were found in quality of the network, frequency of contact, and loneliness in the 18-49 age group, whereas in the 50+ age group significant differences were found in loneliness, size and quality of the network, and frequency of contact. In all cases, the significant differences found were associated with a small effect size. No significant differences in the overall sample (pooling both age groups) were found across countries regarding frequency of contact. In general terms, the health status score (also shown in Table 2) was higher in Finland and lower in Poland. The only pairwise comparison in health status associated with a high effect size was found for the older age group, in which the Finnish sample showed a better health status than the Polish sample.

Table 2. Mean estimates (95% CI) on the components of the social network, the UCLA Loneliness Scale and health status.

Variables				***F***	**d. f.**	***p***	**Hedges' *g***		
	Finland	**Poland**	**Spain**				**F-P** [a]	**F-S** [b]	**P-S** [c]
18-49 years									
Size of the network	9.01 (8.30, 9.72)	8.02 (7.13, 8.92)	9.05 (8.44, 9.67)	1.94	2, 2402	0.14	n.s.	n.s.	n.s.
Frequency of contact	5.21 (5.09, 5.33)	5.31 (5.19, 5.43)	5.13 (5.04, 5.21)	3.01	2, 2402	0.049	n.s.	n.s.	0.13
Quality of the network	5.41 (5.30, 5.52)	5.66 (5.56, 5.76)	5.28 (5.19, 5.36)	16.19	2, 2402	<0.001	0.18	n.s.	0.27
Loneliness	3.50 (3.40, 3.59)	3.70 (3.60, 3.79)	3.60 (3.51, 3.69)	4.03	2, 2402	0.018	0.18	n.s.	n.s.
Health status	74.81 (73.67, 75.96)	71.56 (70.57, 72.55)	75.37(74.54, 76.20)	17.92	2,2402	<0.001	0.28	n.s.	0.32
50+ years									
Size of the network	8.39 (7.91, 8.87)	6.83 (6.46, 7.20)	8.33 (8.01, 8.66)	21.25	2, 7641	<0.001	0.22	n.s.	0.20
Frequency of contact	5.05 (4.97, 5.12)	4.82 (4.74, 4.91)	5.14 (5.09, 5.19)	20.40	2, 7641	<0.001	0.14	n.s.	0.21
Quality of the network	5.49 (5.41, 5.56)	5.53 (5.45, 5.61)	5.33 (5.28, 5.38)	11.59	2, 7641	<0.001	n.s.	0.12	0.13
Loneliness	3.51 (3.45, 3.57)	3.79 (3.73, 3.85)	3.74 (3.68, 3.80)	23.14	2, 7641	<0.001	0.22	0.17	n.s.
Health status	69.82 (69.29, 70.35)	61.34 (60.84, 61.85)	66.16 (65.73, 66.60)	261.72	2,7641	<0.001	0.76	0.30	0.39
Overall sample									
Size of the network	8.74 (8.29, 9.19)	7.50 (6.97, 8.03)	8.74 (8.36, 9.11)	8.15	2, 10045	<0.001	0.18	n.s.	0.16
Frequency of contact	5.14 (5.06, 5.21)	5.10 (5.02, 5.18)	5.13 (5.08, 5.19)	0.33	2, 10045	>0.25	n.s.	n.s	n.s.
Quality of the network	5.44 (5.37, 5.51)	5.60 (5.54, 5.67)	5.30 (5.25, 5.35)	24.25	2, 10045	<0.001	0.10	0.10	0.20
Loneliness	3.50 (3.44, 3.56)	3.74 (3.68, 3,80)	3.66 (3.60, 3.72)	14.88	2, 10045	<0.001	0.19	0.12	n.s.
Health status	72.63 (71.94, 73.31)	67.08 (66.48, 67.68)	71.34 (70.83, 71.84)	86.09	2, 10045	<0.001	0.46	0.10	0.25

Weighted and age-standardized data

[a] Effect size associated with significant differences found in the pairwise comparison between Finland and Poland

[b] Effect size associated with significant differences found in the pairwise comparison between Finland and Spain

[c] Effect size associated with significant differences found in the pairwise comparison between Poland and Spain

n. s. = Significant differences were not found and effect size is not reported

The relationships between the components of the social network (size of the network, frequency of the contact, and quality of the network) and loneliness were assessed in unadjusted analyses by means of a correlation matrix (Table 3). The strongest relationship was found between quality of the network and frequency of contact with members of the network: $r = 0.71$ [95% CI = (0.70, 0.72)]. The correlation between loneliness and size of the network was low ($r = -0.11$), whereas the correlation coefficients between loneliness and quality of the network ($r = -0.24$), and between loneliness and frequency of contact ($r = -0.25$) were moderate.

Table 3. Correlation matrix (95% CI) among size of the network, frequency of contact with members of the network, quality of the network, and the score on the UCLA Loneliness Scale ($n = 10\ 047$).

	Size of the network	**Frequency of contact**	**Quality of the network**	**Loneliness**
Size of the network	1	-	-	-
Frequency of contact	0.14 (0.12, 0.16)	1	-	-
Quality of the network	0.14 (0.12, 0.16)	0.71 (0.70, 0.72)	1	-
Loneliness	-0.11 (-0.13, -0.09)	-0.25 (-0.27, -0.23)	-0.24 (-0.26, -0.22)	1

A hierarchical linear regression model was estimated in each country to assess the differential association of loneliness and the components of the social network with health. Similar results were found across countries (Table 4). A significant increase in the percentage of variance explained was observed when loneliness was added to the model, but not when the block corresponding to the components of the social network was added. The strongest relationships with health were found for age, depression, and loneliness. The association of age with health was different across countries (β = -0.24 in Finland, β = -0.32 in Spain, and β = -0.47 in Poland). In all cases, a higher age, the presence of depression and a higher score on loneliness were associated with a worse health status. In Finland, the effect size associated with the relationship between loneliness and health status was higher (β = -0.25) than in Spain and Poland (β = -0.18 and β = -0.16, respectively). Frequency of contact with members of the network was the only component of the social network having a significant association with health, and it was included in the final multiple linear regression model.

Table 4. Final hierarchical linear regression models predicting health status in each country; weighted data.

	Finland		**Poland**		**Spain**	
Variables	**Coef. (s. e.)**	**β**	**Coef. (s. e.)**	**β**	**Coef. (s. e.)**	**β**
Intercept	81.85 *** (2.30)		81.45 ***(1.82)		81.65 ***(1.58)	
First block						
Gender (Ref. Female)	1.60 ** (0.46)	0.08	1.91 *** (0.45)	0.08	2.49 *** (0.37)	0.10
Age	-0.14 *** (0.02)	-0.24	-0.32 *** (0.02)	-0.47	-0.24 *** (0.01)	-0.32
Married or in a partnership (Ref. Not married or in a partnership)	1.58 (0.88)	0.07	-0.36 (0.69)	-0.01	-0.58 (0.52)	-0.02
Years of education	0.22 ***(0.06)	0.09	0.33 *** (0.07)	0.10	0.33 *** (0.03)	0.17
Residential setting (Ref. Rural)	1.22 * (0.53)	0.05	-0.16 (0.45)	-0.01	1.02 * (0.49)	0.17
Household composition (Ref. Living in a single household)						
Living in a dual household	-2.77 ** (0.91)	-0.13	-1.23 (0.70)	-0.05	-1.62 (0.56)	-0.07
Living in a household with three or more People	-3.30 ** (1.09)	-0.13	-2.91 *** (0.75)	-0.12	-2.47 *** (0.62)	-0.10
Household income (Ref. 1st/2nd quintile)	1.71 ** (0.57)	0.08	1.99 *** (0.49)	0.08	0.73 * (0.36)	0.03
Depression (Ref. No)	-8.71 *** (0.68)	-0.25	-7.79 *** (0.65)	-0.18	-8.32 *** (0.46)	-0.27
Second block, ΔR^2	$\Delta R^2 = 0.003$, n.s.		$\Delta R^2 = 0.006$, n.s.		$\Delta R^2 = 0.004$, n.s.	
Size of the network	-0.02 (0.03)	-0.01	-0.04 (0.03)	-0.02	-0.03 (0.02)	-0.03
Frequency of contact	0.34 (0.23)	0.05	0.60 ** (0.18)	0.08	0.26 (0.20)	0.03
Quality of the network	0.22 (0.23)	0.03	0.05 (0.19)	0.01	0.33 (0.19)	0.04
Third block, ΔR^2	$\Delta R^2 = 0.052$ ||		$\Delta R^2 = 0.022$ ||		$\Delta R^2 = 0.020$ ||	
Loneliness	-2.48 *** (0.21)	-0.25	-1.50 *** (0.15)	-0.16	-1.46 *** (0.12)	-0.18
Adjusted R^2 of the final model	$R^2 = 0.288$		$R^2 = 0.400$		$R^2 = 0.383$	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

|| Indicates significant increase of variance explained at a 99% confidence level.

n.s. Indicates non-significant increase of variance explained at a 95% confidence level.

In the final model shown in Table 5, a high effect associated with the relationship between loneliness and health was found after controlling for covariates. A marginally significant effect for frequency of contact with members of the network was also found. Frequency of contact was associated with better health status. Regarding the other covariates, age (β = -0.47), depression (β = -0.23), and years of education (β = 0.13) presented the strongest correlation with health: higher age and the presence of depression were associated with worse health status, whereas more years of education were associated with better health. Men had a better health status than women (β = 0.13) and living in Finland was associated with better health.

Table 5. Multiple linear regression model with health status as dependent variable; weighted data.

	Coef. (s.e.)	**95% CI**	***t***	**β**
Intercept	93.44 *** (2.04)	(89.44, 97.44)	45.78	-
Gender (Ref. Female)	3.14 *** (0.69)	(1.78, 4.49)	4.54	0.13
Age	-0.33 *** (0.02)	(-0.38, -0.29)	-14.69	-0.47
Years of education	0.32 *** (0.03)	(0.26, 0.37)	11.54	0.13
Residential setting (Ref. Rural)	0.53 (0.29)	(-0.03, 1.09)	1.84	0.02
Household composition (Ref. Living in a single household)				
Living in a dual household	-1.44 *** (0.30)	(-2.02, -0.85)	-4.79	-0.06
Living in a household with three or more people	-2.50 *** (0.35)	(-3.19, -1.82)	-7.18	-0.10
Household income (Ref. $1^{st}/2^{nd}$ quintile)	1.29 *** (0.27)	(0.77, 1.82)	4.84	0.05
Depression (Ref. No)	-8.38 *** (0.33)	(-9.04, -7.73)	-25.11	-0.23
Country (Ref. Finland)				
Poland	-12.27 (1.56)	(-15.33, -9.21)	-7.87	-0.50
Spain	-5.67 (1.54)	(-8.70, -2.64)	-3.67	-0.23
Frequency of contact	0.30 (0.16)	(-0.01, 0.61)	1.89	0.04
Frequency of contact # Poland	0.48 * (0.20)	(0.08, 0.87)	2.37	0.10
Frequency of contact # Spain	0.10 (0.21)	(-0.32, 0.49)	0.48	0.02
Loneliness	-3.72 *** (0.39)	(-4.49, -2.96)	-9.51	-0.41
Loneliness # Poland	1.05 *** (0.25)	(0.56, 1.53)	4.21	0.18
Loneliness # Spain	1.09 *** (0.23)	(0.64, 1.53)	4.79	0.19
Loneliness # Age	0.02 *** (0.01)	(0.01, 0.03)	4.15	0.19
Loneliness # Male	-0.31 (0.17)	(-0.64, 0.02)	-1.84	-0.05

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; Interaction terms between frequency of contact with members of the network and country, between loneliness and country, between loneliness and age, and between loneliness and gender, were considered. Adjusted R^2 of the model = 0.395

According to the interaction terms included in the last regression model, the relationship between frequency of contact with members of the network and health was slightly stronger in Poland than in Finland and Spain (Figure 1). These differences across countries were higher in the case of the relationship between loneliness and health: the association of loneliness with health was stronger in Finland than in the other two countries (Figure 2).

Figure 1. Relationship between frequency of contact with members of the network and health status by country, adjusted for the covariates considered in the multiple linear regression model.

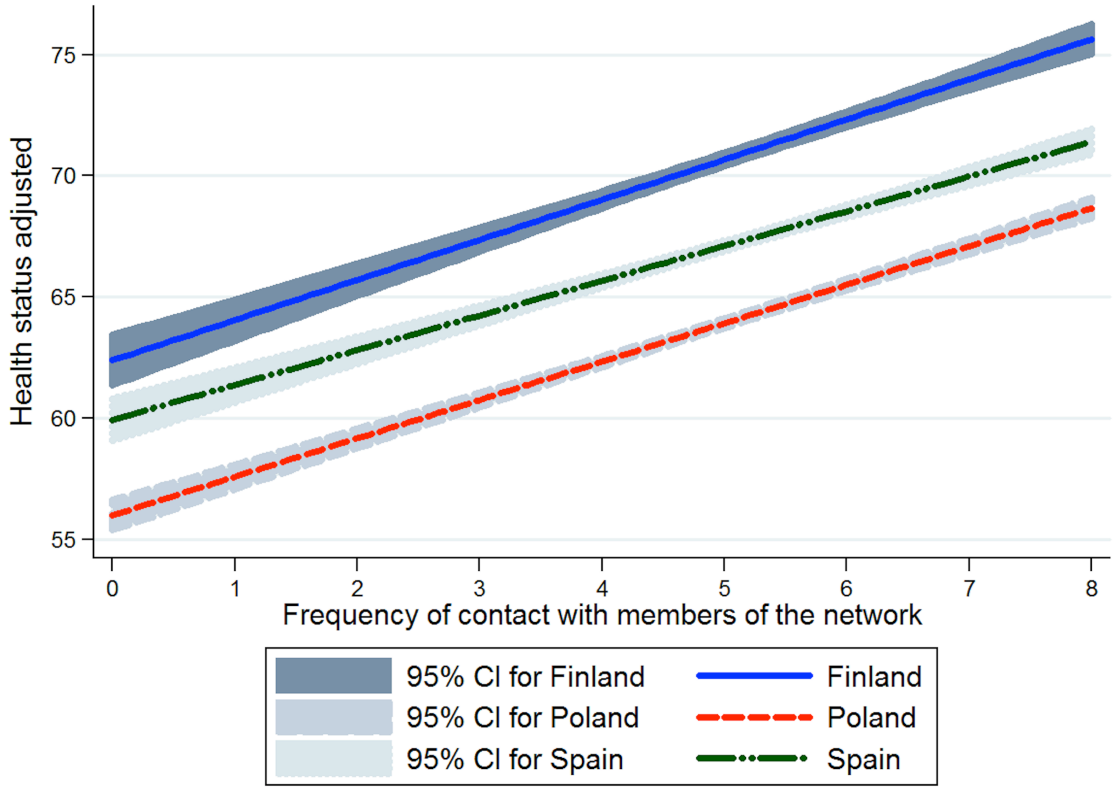
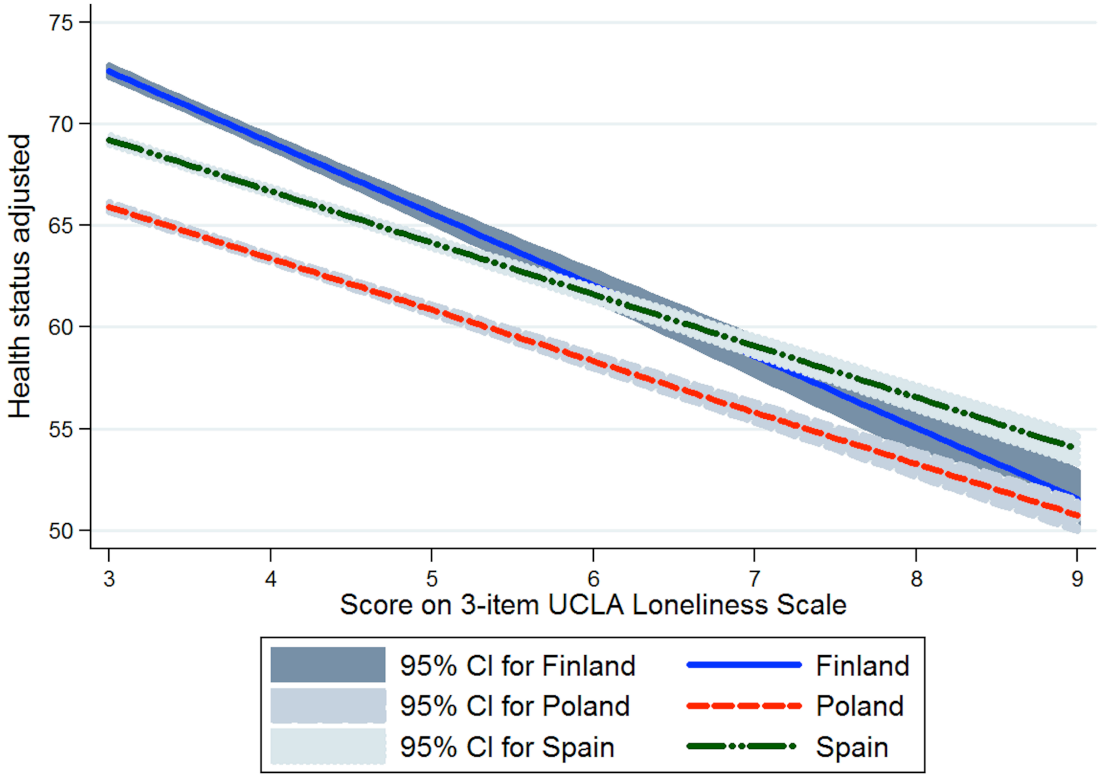
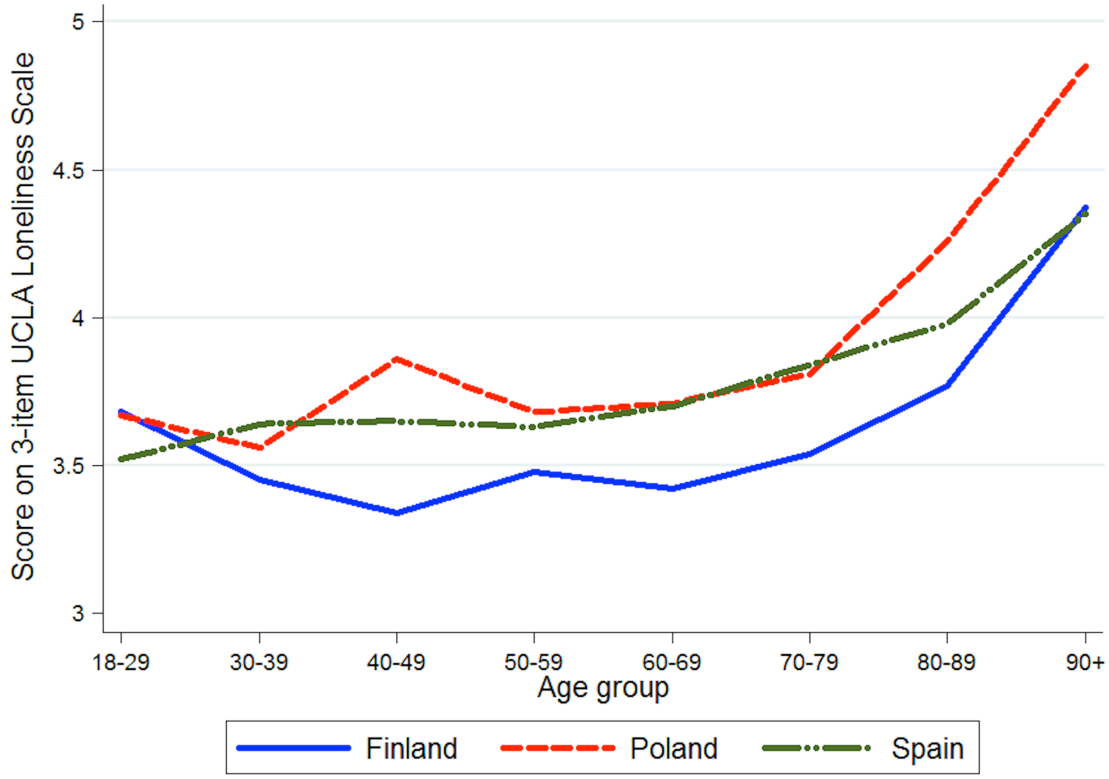


Figure 2. Relationship between loneliness and health status by country, adjusted for the covariates considered in the multiple linear regression model.



As age increased, the relationship between loneliness and health was less strong, while the interaction term between gender and loneliness was not significant, as can be observed in Table 5. In all countries, loneliness mean scores were significantly higher in females than in males, although these differences had small effect sizes: in Finland, 3.55 ± 1.09 for females vs. 3.41 ± 0.94 for males (p = 0.003; Hedges' g = 0.14); in Poland, 3.91 ± 1.35 vs. 3.78 ± 1.28 (p = 0.003; Hedges' g = 0.10); and in Spain, 3.89 ± 1.59 vs. 3.56 ± 1.26 (p < 0.001; Hedges' g = 0.23). Loneliness mean scores by country and age group are shown in Figure 3. Eight different age groups were considered (18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, and 90+) and a rising trend could be observed in the oldest population. Beta coefficients associated with the relationship between age group and loneliness were 0.04 in Finland, 0.11 in Poland, and 0.07 in Spain.

Figure 3. Mean score on 3-item UCLA Loneliness Scale, by country and age group.



Discussion

The results of the present study showed that there was a small or no difference across countries in the mean scores for loneliness and the components of the social network. People aged 50+ from Finland reported slightly lower scores for loneliness than their Polish and Spanish counterparts. This finding is in the line with previous studies suggesting that people from northern European countries tend to be less lonely than their peers in southern and central European countries (24, 54). Financial and socioeconomic aspects (24), as well as the different characteristics of the health and welfare systems (23) could explain the observed differences across countries. The small differences found in the scores in loneliness across countries and between age groups

were similar to those found in previous studies such as the Survey of Health, Ageing and Retirement in Europe (SHARE) (24, 54).

The frequency of contact with members of the network was the only component of the social network having a significant association with health. Fernández-Ballesteros (9) also found a significant correlation between frequency of contact and health in a Spanish sample of people over 65 years. Small differences across countries were found in the relationship between frequency of contact and health, with the association being slightly stronger in Poland than in Finland and Spain. Litwin and Stoeckel (26) also found weak or inconsistent effects of social networks on health outcomes in two different countries.

The results for the present study obtained in all three countries suggest that the subjective perception of loneliness has a strong association with health status, above and beyond what could be explained by covariates such as age, gender, marital status, household size and years of education. Even though this relationship was slightly different across the three countries, previous studies also found differences across countries (54). The relationship between loneliness and health was likewise reported in studies that also used the UCLA Loneliness Scale (13-15). Hawkley and Cacioppo (55) proposed a model that explained how loneliness has physical and mental consequences. According to this model, some effects of loneliness are: impairments in attention, cognition, affect, and behavior that activate genetic, neural and hormonal mechanisms, and modifications in the immune functioning, all of which contribute to adverse health outcomes (morbidity and mortality).

The association of subjective feelings of loneliness with health was clearly stronger than the association of the different components of the social network. These results are consistent with previous evidence suggesting that loneliness contributes more

strongly to health than any aspect of the social network (56). Cacioppo and Cacioppo (6) confirmed that loneliness was associated with health problems and the effects of these problems can contribute to early mortality. Steptoe et al. (42) found that loneliness was associated with more health conditions than social isolation, but when they looked at the association with mortality, social isolation had a stronger impact on mortality than loneliness after controlling for several health indicators. As the authors suggest, the fact that loneliness did not have an impact on mortality after controlling for health indicators could be explained by the strong association between loneliness and baseline health.

In the present study, we found a stronger relationship between loneliness and health in the younger population than in older people. It was also found that the mean score for loneliness was higher in the oldest old. This is similar with the results of a previous study by Pinquart and Sörensen (57). Small differences by gender in the loneliness mean scores were found, as reported in previous studies (58).

To our knowledge, the present study is the first to be carried out with nationally representative samples of several countries using identical methods that disentangled the association of health with different components of the social network and loneliness. Nonetheless, these results must be interpreted with caution and a number of limitations should be borne in mind. Due to its cross-sectional design, the present study is limited by temporality and causality, i.e., it was carried out at a single point in time and gives no indication of the sequence of events—whether an increase in the loneliness level occurred before, during or after the deterioration of the individual's health state. By means of the regression models employed in this study, the dependence of health status on loneliness and social network was described. According to Sokal and Rohlf (59) some evidence regarding the possible causation of changes in health status by changes in loneliness could be obtained. However, this evidence can turn out to be weak,

because due to the design of the study, it cannot determine the cause, effect and directionality of the relationships. Moreover, a deterioration of health status can increase the level of loneliness, with changes in loneliness being affected by changes in health status or by the presence of depression. In the work of Peerenboom et al. (60), it was found that depression (as the independent variable) was associated with loneliness (as a dependent variable) even after controlling for confounding factors. Similarly, a recent review of cross-sectional and longitudinal studies focused on loneliness found that loneliness and depressive symptomatology could act synergistically, since these variables have reciprocal influences over time (61). In addition, the health measure is based on self-reporting. An inherent limitation to the analyses conducted in the present study was that the participants who did not answer the question about their social network or their perception of loneliness were excluded. If a participant was cognitively impaired and not able to respond to the interview, a proxy was asked some questions, but the proxy did not respond to the questions about social networks or loneliness. For this reason, these participants were not included in the present analyses. A socio-demographic comparison was carried out between the included and the excluded samples, and in general terms the differences found had a small associated effect size, indicating that they could be due to the large sample size considered in this study; only high differences in age were found between the included and the excluded sample.

Regarding the response rates, some differences were found across countries. In general terms, even though there are no strict standards, the response rates found in the present study can be considered adequate (62) and similar to the ones found in other general population studies recently conducted in Europe, such as SHARE (global response rate for the ten countries of 61.8%, ranging from 37.6% in Switzerland to 73.6% in France) (63), ELSA (individual response rate of 67%) (64) and TILDA

(household response rate of 62%) (65). The participation was lower in Finland than in the other two countries. This is consistent with a global decrease in response rate there which has been observed in many international epidemiological studies (66). In the NordChild 2011 survey, the response rate in Finland was 48.06%, a similar rate to those found in the same study in other Nordic countries like Iceland (47.53%), Norway (49.41%), and Sweden (45.70%) (67).

The instruments used to measure loneliness and social networks in the present study have been employed in previous studies and have shown adequate reliability. Although the UCLA Loneliness Scale has only three items, it appears to measure overall loneliness quite well (33). The scale can be completed in just a few minutes and is adequate for large population health surveys like COURAGE in Europe. It has also been used in previous studies, such as the English Longitudinal Study on Ageing (ELSA) (41, 68). Regarding the measure of the social networks, previous studies also used the question about the number of contacts in the network (69). Moreover, the Elderly in Linköping Screening Assessment, carried out by Vikström et al. (70) in Sweden, measured closeness with relatives, friends and neighbors as part of the social network. Moreover, the question regarding frequency of contact with the members of the social network has been used in national surveys in Spain to assess how often old people have face-to-face contacts, talk by phone, or exchange letters/e-mails with the members of their network (71). However, it is difficult to compare each component of the social network with previous studies, since they report a total score for the social network, and to our knowledge, ours is the first study that disentangled each component to analyze them individually.

As far as we know, this is also the first study that assesses the differential association of health with the components of the social network and the subjective

perception of loneliness in representative samples from three countries that represent different European regions (31) with different socio-economic and health characteristics and welfare systems (23). This investigation is consistent with the previous literature, which shows the importance in public health of loneliness and the components of the social network. It could be relevant to consider the evaluation and screening of feelings of loneliness, and not only the social network, in persons with health problems. Further longitudinal studies are needed in order to be able to infer causality from the associations found in the present study, and to examine the pathways linking loneliness and social networks to health.

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5.2. Prospective relationship of social isolation and loneliness with the use of healthcare service

† **Title:** Prospective relationship of social isolation and loneliness with the use of healthcare services

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Abstract

Objective: To evaluate whether social isolation and loneliness are prospectively associated with healthcare services use, and to assess whether these associations differ by gender.

Study setting: Household survey based on a nationally representative sample of the Spanish population.

Study design: Longitudinal study. Social isolation and loneliness were measured with the Social Isolation Index and the 3-item UCLA Loneliness Scale, respectively. Information about outpatient and inpatient care use at follow-up was obtained.

Data collection: Baseline data collection took place in 2011-2012, with a follow-up in 2014-2015. A total of 2528 adults were interviewed face-to-face. Multiple logistic regressions were run.

Principal findings: Loneliness (odds ratio [OR]=1.12, 95% confidence interval [CI]=1.02-1.24), being unmarried (odds ratio [OR]=0.70, 95% confidence interval [CI]=0.49-0.99) and having less than monthly contact with other family members (odds ratio [OR]=2.08, 95% confidence interval [CI]=1.12-3.85) were associated with a higher frequency of outpatient visits in women. For men neither loneliness nor social isolation were significant. Neither social isolation nor loneliness were associated with inpatient care use.

Conclusions: The results suggest the need to analyse whether programmes for prevention and management of loneliness would also reduce healthcare utilization in women.

Keywords: social isolation, loneliness, healthcare utilization, inpatient care use, outpatient care use.

Introduction

People can live relatively solitary lives and not feel lonely or, on the contrary, they can have a rich social life but feel lonely. The term loneliness is therefore used to refer to a subjective perception, while social isolation refers to an objective social aspect (Cacioppo and Cacioppo 2014; Miller 2011). Even though both constructs are similar they refer to different aspects and show distinct associations with healthcare services use (Bellido-Zanin et al. 2015; Cheng 1992; Ellaway, Wood, and Macintyre 1999; Iliffe et al. 2007).

A previous study found that lonely people visit the general physician more often than non-lonely people (Ellaway et al. 1999). Cheng (1992) showed that loneliness contributes to explain healthcare use and to identify frequent users, even after controlling for health conditions. Among elderly people, loneliness is also positively associated with visits to the physician (Cheng 1992; Gerst-Emerson and Jayawardhana 2015).

Regarding social isolation, some studies found no association between social isolation and hospital admissions, primary care use or outpatients' appointments in elderly people from London (Iliffe et al. 2007), whereas others found that social isolation predicted the use of mental health resources in patients with severe mental disorders (Bellido-Zanin et al. 2015). Moreover, hospital readmission was more frequent in people with a poor social network (Mistry et al. 2001; Rodriguez-Artalejo et al. 2006).

The inconsistency of the results regarding the use of healthcare services in the literature might be influenced by differences in the organization of the healthcare system in each country and differences in social isolation and loneliness across

countries, which implies that the results cannot be extrapolated from one country to another and suggests the need for country-specific analysis.

Furthermore, it is important to study this relationship by gender, since previous studies have reported differences in the number of visits to primary healthcare (Carretero et al. 2014). Zielinski and Halling (2015) found that Swedish men had 26% lower odds of using healthcare services than women. A study carried out in 29 European countries showed gender differences in mental healthcare use, with women having a higher use in some countries, attributable to social roles, family and socioeconomic characteristics (Buffel, Van de Velde, and Bracke 2014). In addition, gender differences have also been found in subjective feelings of loneliness and in social isolation. Dahlberg et al. (2015) explain that gender should always be taken into consideration when attempting to understand loneliness, since the risk of this feeling is higher in women than in men. Another study showed that women are better able to form new social networks while men have smaller networks (Dykstra and Fokkema 2007) and receive less social support (Pinquart and Sörensen 2001) .

Further investigation on the association of social isolation and loneliness with outpatient and inpatient care use is needed. Additionally, the present study aims to evaluate which aspects of social isolation are more frequently associated with outpatient and inpatient care use; as well as to examine whether these associations differ by gender.

The hypotheses postulated are: a) social isolation and loneliness are associated with outpatient and inpatient care use; b) the relationship between the aforesaid variables and healthcare use will be significant in women and in men.

Methods

Study population and design

Data used in these analyses were obtained from a longitudinal study on a nationally representative sample from the Spanish adult population. The baseline data collection was part of the Collaborative Research on Ageing in Europe (COURAGE in Europe) (http://www.courageineurope.eu) (Leonardi et al. 2014), a survey conducted using nationally representative samples of non-institutionalized adults aged 18+ years in three European countries (Finland, Poland and Spain) between April 2011 and May 2012. A second wave was carried out between December 2014 and June 2015 in Spain. The mean follow-up was 3.25 years (SD=0.18). In both waves participants were interviewed face-to-face at their own homes with Computer-Assisted Personal Interviewing by trained staff. Quality assurance procedures were implemented during fieldwork (Üstun et al. 2005). To obtain a nationally representative sample in the first wave, a stratified multistage random sampling method was used with strata defined according to the Spanish regions and population size.

The overall sample of the first wave comprised 4753 participants in Spain, whereas in the follow-up 2528 of these participants were re-interviewed. The individual response rates were 69.9% at baseline and 69.5% for the follow-up. The ethics review committees of Parc Sanitari Sant Joan de Déu, Barcelona and La Princesa University Hospital, Madrid, approved the baseline and the follow-up studies. Written informed consent from each participant was also obtained.

Study variables

Social isolation. Social isolation was measured with a Social Isolation Index (Shankar et al. 2011) that assigned one point if the respondent was unmarried/not cohabiting; another point if he or she had less than monthly contact with children or did

not have children; a third point if he or she had less than monthly contact with other family members or did not have other family members; a fourth point if he or she had less than monthly contact with friends or did not have friends; and a fifth point if he or she did not participate in organizations, social clubs or groups, religious services, or committees. The score in the Social Isolation Index, originally ranging from 0 to 5, was dichotomized using the cut-off point 3+ suggested by Beach and Bamford (2014) to represent the greatest social isolation. Participants with social isolation scores ranging from 0 to 2 were considered as less socially isolated.

Loneliness. Loneliness was assessed as a continuous variable by means of the 3-item UCLA Loneliness Scale (Hughes et al. 2004). This scale comprises the following items: "*How often do you feel that you lack companionship?", "How often do you feel left out?"* and "*How often do you feel isolated from others?"*, which are assessed on a 3-point scale (1 = hardly ever; 2 = some of the time; 3 = often). The UCLA Loneliness Scale has shown satisfactory reliability and both concurrent and discriminant validity (Hughes et al. 2004). The scale showed acceptable internal reliability in the present study (Cronbach's alpha = 0.89; mean inter-item correlation = 0.72). The scores for each item were added up to produce a loneliness score ranging from 3 to 9, with higher scores indicating higher loneliness levels.

Use of healthcare services. Both outpatient and inpatient hospital care use were evaluated in both waves, by asking about the number of times that the participant had received outpatient healthcare or medical consultation, and if they had stayed overnight in a hospital or in a long-term care facility in the previous 12 months, respectively. For outpatient care use, a dichotomized variable was created. Participants who reported from 0 to 5 visits were classified as "infrequent or moderate outpatient care use", while those with 6+ visits were defined as "frequent outpatient care use". Inpatient care use

was also dichotomized as: use (at least one overnight stay in a hospital in the previous 12 months) and not use (no overnight stays in a hospital in the previous 12 months).

Other variables: Information about age (years), gender, education (number of years in full time education), and employment (as currently working vs. not working) was also obtained. Comorbidities (i.e. osteoarthritis, angina pectoris, stroke, diabetes, chronic lung disease, asthma, depression and hypertension) at baseline were defined through self-reported diagnosis. The incidence of comorbidities was measured as the number of new diseases that the participant developed during the follow-up. The presence of a depressive episode during the previous 12 months was assessed with a set of questions based on the World Mental Health Survey version of the Composite International Diagnostic Interview (Kessler and Üstün 2004). Individuals were considered to have had a depressive episode if they had been diagnosed with depression and had been taking medication or receiving some other treatment (e.g. psychotherapy) during the previous 12 months, or if they reported the presence of the core symptoms of the condition during the previous 12 months, according to DSM-IV (American Psychiatric Association 1994). The presence of limitations in Activities of Daily Living (ADLs) and the presence of limitations in Instrumental Activities of Daily Living (IADLs) were considered at baseline. ADLs describe a set of daily self-care activities and assess the need for help with personal care activities, whereas IADLs correspond to a higher-level functioning considered necessary to live independently. Incidence variables were created for limitations in ADLs and limitations in IADLs: a participant presented incident limitation in ADLs if he/she did not have limitations at baseline but had limitations in ADLs at the follow-up; a participant presented incident limitations in IADLs if he/she did not have limitations at baseline but had limitations in IADLs at the follow-up.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the sample. Differences in socio-demographics based on gender and in the sample included and excluded from the analyses were also assessed, reporting effect sizes when significant differences at the 95% confidence interval were found. Cramer's *V* was used for comparing frequencies in categorical variables (chi-square test), while Hedges' *g* was employed for comparing mean scores in continuous variables. Cohen's guidelines (Cohen 1988) were used as a standard to evaluate the magnitude of the effect size. Cramer's *V* values of 0.10, 0.30, and 0.50 constitute small, medium, and large effect sizes; whereas Hedges' *g* values of 0.20, 0.50, and 0.80, constitute small, medium, and large effect sizes, respectively.

The prospective relationship between social isolation and loneliness with inpatient and outpatient care use was evaluated by means of logistic regression analyses. All analyses were conducted separately for women and men. Odds ratios (OR) and 95% Confidence Intervals (CIs) were reported. Baseline and follow-up factors related to frequent use of outpatient care and the use of inpatient care services in the 12 months before the interview were evaluated. Logistic regressions were conducted hierarchically.

Firstly, to assess the relationship with inpatient care use, the analyses included loneliness and social isolation simultaneously, and adjusted for age and years of education in the first model; while a second model additionally adjusted for socio-demographic characteristics, medical comorbidities, limitations in ADLs, limitations in IADLs, outpatient and inpatient care use at baseline, incidence of limitations in ADLs, incidence of limitations in IADLs, and incidence of comorbidities in the follow-up. Subsequently, two more models were run including loneliness and the five components of the Social Isolation Index simultaneously. Again, in this case, a first model adjusted

for age and years of education, while a second one adjusted also for the rest of covariates described above.

Similar analyses were carried out for inpatient care use. All the analyses were done using Stata SE version 11 (StataCorp 2011).

Results

The final sample included in the analyses comprised 2410 individuals after excluding those who could not be followed up (n = 2225) and those who did not answer the questions about social isolation or the items of the UCLA Loneliness Scale (n = 118). The baseline characteristics of the included and excluded individuals are shown in Table 1. After comparing baseline characteristics in both samples, the main significant differences were found for age ($p < 0.001$, Hedges' g =0.13), years of education ($p < 0.001$; Hedges' $g = 0.13$), and social isolation ($p = 0.010$, Cramer's $V = 0.06$); as shown, the effects sizes associated were small in all cases. Mean age of the final sample included was 59.43 years (SD = 15.43) at baseline, with 1310 (54.3 %) women. The age of the sample ranged from 18 to 98 years at baseline. A total of 21.3% of participants had frequent use of outpatient care and 21.7% had been hospitalized in the 12 months before the baseline interview, whereas 19.6% had frequent outpatient care use and 11% had been hospitalized in the 12 months before the follow-up interview. A total of 1353 (56.1%) respondents did not participate in organizations, social clubs or groups, religious services or committees, whereas 163 (6.8%) participants had less than monthly contact with family. The mean loneliness score was 3.71 (SD = 1.43). Based on gender, significant differences were found in frequent outpatient care use, comorbidities, presence of limitations in ADLs, limitations in IADLs, employment, the Social Isolation Index and its components (e.g. being unmarried, having less than monthly contact with children, with friends and no participation), although the effect sizes associated

(Cramer's *V* values) tended to be small, with values ranging from 0.05 to 0.23. Significant differences in years of education (11.52 ± 6.52 in males vs. 10.93 ± 6.28 in females; p=0.025, Hedges' g = 0.11) and in the UCLA Loneliness Scale (3.55 ± 1.26 in males vs. 3.85 ± 1.54 in females; p <0.001, Hedges' g= 0.22) were also found based on gender although they had a small effect size associated.

As shown in Table 2, the relationship between social isolation as a dichotomous variable and frequent outpatient care use was not significant for women or for men, after controlling for potential confounders. In contrast, loneliness was significantly associated with frequent outpatient care use in women after controlling for socio-demographic variables, employment, comorbidities, limitations in ADLs, limitations in IADLs, baseline information about outpatient and inpatient care use, incidence of limitations in IADL, incidence of limitations in ADL, and incidence of comorbidities (OR = 1.12, 95% CI = 1.02-1.23; p= 0.019). This relationship was not significant in men.

When the components of the Social Isolation Index were analysed separately (Table 3), being unmarried (OR = 0.70, 95% CI = 0.49-0.99; p= 0.042) and having less than monthly contact with other family members (OR = 2.08, 95% CI = 1.12-3.85; p= 0.020) were the only items associated with frequent outpatient care use in women after adjusting by all covariates. No associations were found in men. Loneliness was associated with frequent outpatient care use in women after adjusting for age and years of education (OR = 1.16, 95% CI = 1.07-1.27; p = 0.001), and adding other covariates (OR = 1.15, 95% CI = 1.04-1.27; p= 0.006). For men, loneliness was not significantly associated with outpatient care use.

No associations between social isolation and loneliness with inpatient care use were found (Tables 4 and 5).

Discussion

The results found in the present study showed that loneliness, and two items of the Social Isolation Index, being unmarried and having less than monthly contact with other family members or not having other family members, were prospectively associated with a frequent outpatient care use in women. Additionally, neither loneliness nor social isolation were related to inpatient care use in women or in men.

Most of the participants had contact with their families more than once a month. This could be explained because in European Mediterranean countries, especially Spain, people usually have close and frequent contact with the family. In this region the family ties are relatively strong: the process of leaving the parental household can be delayed until after marriage, grandparents often live near their sons and daughters to give support, and families care of the elderly by carrying out the traditional role of attending to their needs (Reher 1998). In contrast, people from northern European countries, which are more individualistic, tend to feel less lonely than their peers in southern and central European countries with higher rates of familism (Dykstra 2009). On the other hand, few people reported participation in organizations, social clubs or groups, religious services, or committees. According to Rodriguez-Artalejo et al. (2006), the participation of Spanish elderly people in social events and groups is not as frequent as in other countries.

In line with previous results (Redondo-Sendino et al. 2006), this study found that women use outpatient care services more frequently than men. More negative attitudes towards care-seeking among men (Buffel et al. 2014), and men's tendency to use health services only for severe complaints (Leaf and Bruce 1987), could also explain this difference. No significant differences were found in inpatient care use between men and women.

Moreover, loneliness was associated with frequent use of outpatient care services in women, but not in men. More frequent use of outpatient care among those who feel lonely could be due to the fact that the doctor-patient relationship may be a source of support given that the physician is considered a familiar person to talk with (Cheng 1992), or someone with whom the person can have interaction or interpersonal stimulation (Gerst-Emerson and Jayawardhana 2015). Regarding social isolation, when the index was disentangled, only two out of five items were associated with frequent outpatient care use: being married and having less than monthly contact with other family members in women. For men, social isolation measured as an index and disentangling all its components was not associated with use of outpatient care services. These results are contrary to previous studies that found that social isolation was not associated with greater use of medical services (Iliffe et al. 2007; Lasebikan, Owoaje, and Asuzu 2012). This could be because in previous research social isolation has been analysed as a global score and was not disentangled to study the association of each specific aspect with healthcare use. The inconsistency of the results might also be partially explained by the different organization of the healthcare system in each country and differences in social isolation and loneliness across countries. Spain has a national health system, financed mainly by general taxes that include primary care, specialized care and access to healthcare services without patient cost sharing. Only a small part of healthcare services are not covered by the national system, such as dental care (Garrido-Cumbrera et al. 2010). Regarding the disparity across countries, Rico-Uribe et al. (2016) found differences in social networks and loneliness between Finland, Poland and Spain. In line with this, it might be that the above-mentioned differences together with diversity in expectations about social relationship in collectivistic and individualist countries could influence the use of healthcare across countries. Gender

differences in the association of loneliness and social isolation with healthcare use could be explained as a result of differential life situations of men and women. For example, women live longer than men and tend to marry men older than themselves (Lennartsson and Lundberg 2007), meaning that there are greater levels of widowhood among women whom might use the health services to find social support or social contact. Finally, in a large study of 10,842 participants younger than 65, in which help-seeking attitudes and behaviour were analysed, it was found that one of the factors more strongly associated with some form of help-seeking was being a woman, and that a possible reason for consulting the primary care physician more frequently was having a weak social support and few social contacts (Oliver et al. 2005).

Even though there are no previous studies that analysed the relationship between loneliness and social isolation with the healthcare use together, most of the studies that focused on loneliness suggest that lonely people visit the health services frequently (Cheng 1992; Ellaway et al. 1999; Hall and Havens 1999; Newall, McArthur, and Menec 2015), in contrast with studies that only focused on social isolation, in which contradictory results are found: some articles found an association (Ellaway et al. 1999; Longman et al. 2012) and others did not (Iliffe et al. 2007; Lasebikan et al. 2012). A possible explanation might be that a socially isolated person could be comfortable in that situation and might not desire social contact, whereas loneliness is a disturbing feeling and the person might want to improve social networks and social support.

Regarding the relationship of loneliness and social isolation with inpatient care use, and contrary to the hypothesis postulated, there were no differences based on gender, and neither loneliness nor social isolation were associated with hospitalization. Previous studies have also found that loneliness is associated with physician visits but not hospitalizations (Gerst-Emerson and Jayawardhana 2015). One reason could be that

while the decision to visit the physician depends on the patient, the decision about hospitalization depends mainly on the physician. Moreover, patients develop a stronger social connection with someone they visit frequently, such as their general practitioner, rather than hospital staff whom they see less frequently (Gerst-Emerson and Jayawardhana 2015).

To our knowledge, the present study is the first that is based on a nationally representative sample of Spanish adults to analyse whether social isolation and loneliness are associated with the use of healthcare services. In addition, this study analysed social isolation in two different forms: as an index, and considering each component individually. Nonetheless, limitations of this study should also be noted. First, the healthcare service use was self-reported, which may result in recall or reporting bias. Second, the questions about the use of healthcare services were referring to the 12 months before the follow-up interview and did not include the full follow-up period (3 years), which means that the first two years of the follow-up period were not evaluated. Third, some participants were excluded from these analyses because: a) they had poor health status and could not respond to the interview by themselves, so their information was obtained through a proxy respondent who did not answer the social isolation and loneliness questions; b) they ended the interview before answering the social isolation, loneliness and healthcare services questions that appeared at the end of the survey; c) they did not respond to some of the questions and hence had missing data, or d) they did not participate in the follow-up interview because they passed away during the follow-up period, could not be located, or refused to participate. Fourth, the healthcare use variables were dichotomized. However, there is not a clear consensus about the cut-off point for these variables, especially for frequent and infrequent use of outpatient care. Fifth, the sample only covered people who were not institutionalized at

baseline. Further research could explore these associations in institutionalized adults, who may have high levels of loneliness and social isolation. Studies analysing the impact of gender differences on the association of loneliness and social isolation with healthcare by subgroups of different diseases are also needed. Moreover, future studies should analyse visits to the general physician and specialized care visits separately.

The results of this study suggest the need to analyse whether programmes for the prevention and management of loneliness would also reduce healthcare utilization in women. Training health professionals to identify patients' social needs, intervene among those who are lonely and transfer them to the adequate service would not only benefit the patients, but might also reduce the use of healthcare services. Finally, there is a need to further investigate the use of healthcare services and to strengthen the collaboration between social and health services, since it is possible that the people who do not seek help might have an increased risk of having a health problem, while on the other hand people who use the health services frequently may use the services for social reasons. Furthermore, gender differences and cultural aspects should also be examined.

Table 1. Baseline characteristics of the included and excluded sample and by gender.

	Included sample	**Excluded sample**	**Effect size [a]**	**Female (Sample included)**	**Male (Sample included)**	**Effect size [b]**
Number of participants	2410	2343	-	1310	1100	-
Age, Mean ± SD	59.43 ± 15.43	61.48 ± 16.97	0.13	59.84 ± 15.71	58.94 ± 15.09	n.s.
Years of education, Mean ± SD	11.20 ± 6.40	10.41 ± 6.11	0.13	10.93 ± 6.28	11.52 ± 6.52	0.10
Outpatient care use at baseline: n (%)			n.s.			0.12
Infrequent or moderate use	1874 (78.70)	1791 (77.30)		959 (74.05)	915 (84.18)	
Frequent use	508 (21.30)	526 (22.70)		336 (25.95)	172 (15.82)	
Inpatient care use at baseline: n (%)			n.s.			n.s.
No use of inpatient care	1866 (78.34)	1760 (75.96)		1006 (77.68)	860 (79.12)	
Use of inpatient care	516 (21.67)	557 (24.04)		289 (22.32)	227 (20.88)	
Presence of comorbidities: n (%)						
Osteoarthritis	600 (24.90)	561 (23.94)	n.s.	447 (34.12)	153 (13.91)	0.23
Angina pectoris	133 (5.52)	127 (5.42)	n.s.	55 (4.20)	78 (7.09)	0.06
Stroke	82 (3.40)	101 (4.31)	n.s.	41 (3.13)	41 (3.73)	n.s.
Diabetes	338 (14.02)	323 (13.79)	n.s.	162 (12.37)	176 (16.00)	0.05
Chronic lung disease	178 (7.39)	161 (6.87)	n.s.	100 (7.63)	78 (7.09)	n.s.
Asthma	174 (7.22)	161 (6.87)	n.s.	114 (8.70)	60 (5.45)	0.06
Depression	414 (17.18)	387 (17.47)	n.s.	300 (22.90)	114 (10.36)	0.17
Hypertension	785 (32.61)	797 (34.13)	n.s.	457 (34.97)	328 (29.82)	0.05
Presence of limitations in ADLs: n (%)	209 (8.67)	188 (8.65)	n.s.	146 (11.15)	63 (5.73)	0.10
Presence of limitations in IADLs: n (%)	276 (11.45)	248 (11.41)	n.s.	183 (13.97)	93 (8.45)	0.09
Currently working: n (%)	729 (30.25)	541 (31.15)	n.s.	350 (26.72)	379 (34.45)	0.08
Score on the Social Isolation Index: n (%)			0.06			0.10
0	524 (21.74)	433 (19.97)		250 (19.08)	274 (24.91)	
1	999 (41.45)	839 (38.70)		544 (41.53)	455 (41.36)	
2	569 (23.61)	533 (24.58)		352 (26.87)	217 (19.73)	
3	268 (11.12)	300 (13.84)		140 (10.69)	128 (11.64)	

4	47 (1.95)	56 (2.58)		22 (1.68)	25 (2.27)	
5	3 (0.12)	7 (0.32)		2 (0.15)	1 (0.09)	
Items of the Social Isolation Index: n (%)						
Unmarried	922 (38.26)	986 (42.08)	0.04	620 (47.33)	302 (27.45)	0.20
Less than monthly contact with children	508 (21.08)	507 (23.33)	n.s.	249 (19.01)	259 (23.55)	0.06
Less than monthly contact with other family members	163 (6.76)	188 (8.65)	0.04	79 (6.03)	84 (7.64)	n.s.
Less than monthly contact with friends	198 (8.22)	213 (9.80)	n.s.	130 (9.92)	68 (6.18)	0.07
No participation	1353 (56.14)	1279 (58.99)	n.s.	688 (52.52)	665 (60.45)	0.08
Score on UCLA Loneliness Scale, Mean ± SD	3.71 ± 1.43	3.75 ± 1.44	n.s.	3.85 ± 1.54	3.55 ± 1.26	0.22

Note: The sums of the frequencies of some data do not equal the total number of participants due to missing data; the effect size was reported for significant differences found: Cramer's *V* was employed for χ^2 tests to measure association between categorical variables, while Hedges' *g* was used for the comparison of means (unpaired *t*-test) between quantitative variables; n.s. no significant differences; ADLs: Activities of Daily Living; IADLs: Instrumental Activities of Daily Living.

a. Effect size associated to the differences between the sample included and excluded in the analyses.

b. Effect size associated to the differences between the female and male sample.

Table 2. Odds ratios (95% CI) associated with the relationship of social isolation and loneliness with frequent outpatient care use

	Women		Men	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Social Isolation Index (Ref. Less socially isolated)	0.85 (0.54-1.36)	0.81 (0.47-1.37)	1.08 (0.61-1.89)	1.03 (0.54-1.96)
Loneliness	1.14** (1.05-1.24)	1.12 *(1.02-1.24)	1.05 (0.93-1.20)	0.92 (0.78-1.08)

Note: Social isolation and loneliness were simultaneously introduced in all models.
Model 1 adjusted for baseline values in age and years of education; Model 2 adjusted for baseline values in age, years of education, employment (Ref. yes), limitations in ADL (Ref. no limitations), limitations in IADL (Ref. no limitations), osteoarthritis (Ref. no), angina pectoris or/and stroke (Ref. no), diabetes (Ref. no), chronic lung disease or/and asthma (Ref. no), depression with need for treatment (Ref. no), hypertension (Ref. no), inpatient care use at baseline (Ref. no inpatient care use), frequent outpatient care use at baseline (Ref. no frequent outpatient care use), incidence of limitations in IADL (Ref. yes), incidence of limitations in ADL (Ref. yes), and incidence of comorbidities.
The Odds Ratio represents the increased risk per unit gain in loneliness score.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 3. Odds ratios (95% CI) associated with the relationship of the components of the social isolation index and loneliness with frequent outpatient care use.

	Women		Men	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Components of Social Isolation Index				
Unmarried (Ref. married or cohabiting)	0.80 (0.59-1.10)	0.70 * (0.49-0.99)	1.10 (0.66-1.83)	1.15 (0.62-2.11)
Less than monthly contact with children (Ref. more than monthly contact)	0.78 (0.50-1.19)	0.91 (0.56-1.46)	1.23 (0.72-2.12)	1.18 (0.61-2.25)
Less than monthly contact with other family members (Ref. more than monthly contact)	1.67 (0.95-2.95)	2.08 *(1.12-3.85)	1.15 (0.61-2.15)	1.54 (0.75-3.14)
Less than monthly contact with friends (Ref. more than monthly contact)	0.92 (0.57-1.48)	0.85 (0.49-1.46)	1.71 (0.93-3.14)	0.99 (0.47-2.07)
No participation (Ref. participation)	0.91 (0.68-1.22)	0.86 (0.62-1.19)	0.85 (0.60-1.21)	0.84 (0.56-1.26)
Loneliness	1.16**(1.07-1.27)	1.15** (1.04-1.27)	1.03 (0.89-1.18)	0.89 (0.74-1.06)

Note: The five components of the Social Isolation Index and loneliness were simultaneously introduced in all models.
Model 1 adjusted for baseline values in age and years of education; Model 2 adjusted for baseline values in age, years of education, employment (Ref. yes), limitations in ADL (Ref. no limitations), limitations in IADL (Ref. no limitations), osteoarthritis (Ref. no), angina pectoris or/and stroke (Ref. no), diabetes (Ref. no), chronic lung disease or/and asthma (Ref. no), depression with need for treatment (Ref. no), hypertension (Ref. no), inpatient care use at baseline (Ref. no inpatient care use), frequent outpatient care use at baseline (Ref. no frequent outpatient care use), incidence of limitations in IADL (Ref. yes), incidence of limitations in ADL (Ref. yes), and incidence of comorbidities.
The Odds Ratio represents the increased risk per unit gain in loneliness score.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 4. Odds ratios (95% CI) associated with the relationship of social isolation and loneliness with inpatient care use

	Women		Men	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Social Isolation Index (Ref. Less socially isolated)	0.91 (0.50-1.65)	0.74 (0.36-1.51)	1.21 (0.67-2.20)	1.08 (0.57-2.05)
Loneliness	0.97 (0.86-1.09)	0.89 (0.77-1.02)	0.99 (0.85-1.15)	0.95 (0.80-1.13)

Note: Social isolation and loneliness were simultaneously introduced in all models.
Model 1 adjusted for baseline values in age and years of education; Model 2 adjusted for baseline values in age, years of education, employment (Ref. yes), limitations in ADL (Ref. no limitations), limitations in IADL (Ref. no limitations), osteoarthritis (Ref. no), angina pectoris or/and stroke (Ref. no), diabetes (Ref. no), chronic lung disease or/and asthma (Ref. no), depression with need for treatment (Ref. no), hypertension (Ref. no), inpatient care use at baseline (Ref. no inpatient care use), frequent outpatient care use at baseline (Ref. no frequent outpatient care use), incidence of limitations in IADL (Ref. yes), incidence of limitations in ADL (Ref. yes), and incidence of comorbidities.
The Odds Ratio represents the increased risk per unit gain in loneliness score.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

Table 5. Odds ratios (95% CI) associated with the relationship of the components of the social isolation index and loneliness with inpatient care use

	Women		Men	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Components of Social Isolation Index				
Unmarried (Ref. married or cohabiting)	0.94 (0.63-1.41)	0.88 (0.56-1.37)	1.53 (0.90-2.59)	1.61 (0.91-2.87)
Less than monthly contact with children (Ref. more than monthly contact)	1.27 (0.76-2.11)	1.36 (0.76-2.43)	0.82 (0.46-1.48)	0.70 (0.37-1.34)
Less than monthly contact with other family members (Ref. more than monthly contact)	0.61 (0.24-1.58)	0.63 (0.21-1.90)	1.39 (0.73-2.66)	1.56 (0.77-3.17)
Less than monthly contact with friends (Ref. more than monthly contact)	0.90 (0.49-1.64)	0.72 (0.36-1.47)	1.42 (0.72-2.78)	1.19 (0.54-2.60)
No participation (Ref. participation)	1.32 (0.91-1.93)	1.12 (0.73-1.72)	1.06 (0.72-1.54)	0.98 (0.65-1.48)
Loneliness	0.97 (0.86-1.09)	0.89 (0.78-1.03)	0.94 (0.80-1.11)	0.89 (0.74-1.07)

Note: The five components of the Social Isolation Index and loneliness were simultaneously introduced in all models.
Model 1 adjusted for baseline values in age and years of education; Model 2 adjusted for baseline values in age, years of education, employment (Ref. yes), limitations in ADL (Ref. no limitations), limitations in IADL (Ref. no limitations), osteoarthritis (Ref. no), angina pectoris or/and stroke (Ref. no), diabetes (Ref. no), chronic lung disease or/and asthma (Ref. no), depression with need for treatment (Ref. no), hypertension (Ref. no), inpatient care use at baseline (Ref. no inpatient care use), frequent outpatient care use at baseline (Ref. no frequent outpatient care use), incidence of limitations in IADL (Ref. yes), incidence of limitations in ADL (Ref. yes), and incidence of comorbidities.
The Odds Ratio represents the increased risk per unit gain in loneliness score.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$

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5.3. Gender differences in the association of loneliness with mortality: A meta-analysis

† Title: Gender Differences in the Association of Loneliness with Mortality: A Meta-Analysis

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Abstract

Introduction: Loneliness has social and health implications. The aim of this article is to evaluate the association of loneliness with mortality.

Methods: Pubmed, PsycINFO, CINAHL and Scopus databases were searched through June 2016 for published articles that measured loneliness and mortality. The main characteristics and the effect size values of each article were extracted. Moreover, an evaluation of the quality of the articles included was also carried out. A meta-analysis was performed firstly with all the included articles and secondly separating by gender, using a random effects model.

Results: 34 articles involving 50668 participants were included in the systematic review. Loneliness has a trend to be a risk factor for mortality (pooled HR = 1.22; 95% CI = 1.10, 1.35, p = <0.001) for both genders together, and for women and men separately (pooled HR = 1.26; 95% CI = 1.07, 1.48, p = 0.005 for women and pooled HR = 1.45; 95% CI = 1.17, 1.80, p = 0.001 for men).

Conclusions: Loneliness shows a trend to be a risk for mortality and this effect is slightly stronger in men than in women, but the trend disappears when the studies control by health status or comorbidities. More articles that use validated questionnaires for loneliness and that control by health confounders are needed.

Keywords: loneliness, mortality, longitudinal study, meta-analysis.

Introduction

Loneliness has been conceptualized as an individual's subjective experience about the generalized lack of satisfying human relationships [1]. A recent article has shown that the prevalence of loneliness in European countries ranks from 10% in Western and Northern countries to 55% in Eastern countries [2]. Moreover, a report conducted in the United Kingdom suggested that if loneliness is not considered as a relevant priority, in 2030 depression and other health problems may increase, given their association with loneliness [3].

According to previous articles, loneliness has become a serious issue for public health in view of its significant implications with several physical and mental health issues such as: depression [4, 5], alcoholism [6], cardiovascular problems [7], sleep difficulties [7], alteration in the immunological system [8], Alzheimer´s disease [9], and health status in general [10]. Moreover, an increasing body of research has shown that loneliness is also associated with early mortality [11-14].

In order to have a better understanding of the association of loneliness with mortality, gender analyses should be carried out for several reasons. Firstly, women live generally longer than men [15]. Secondly, some studies have shown that feelings of loneliness might be more prevalent in women than in men [16]. Thirdly, women and men build social networks in a different way, as an example, men experience smaller social networks [17] and less intimate relationships [18]. Fourthly, it is culturally less acceptable for men to express their emotions than it is for women [19]. And last but not least, some common risk factors for loneliness are also gender specific, i.e.; depression is more prevalent in women than men [20] whereas alcoholism is more frequent in men [21]. Moreover, the longer life expectancy of women entails that some risk factors for

loneliness such as living alone and widowhood, occur earlier in women than in men [22].

There is a lack of research on the gendered aspects of the association of loneliness with mortality. To our knowledge, no meta-analysis that studies this association by gender has been carried out yet, and this is problematic because what could be associated with mortality for the whole sample might not be for men or women separately. One recent meta-analysis analyzed the impact of loneliness on mortality in men and women together [23]. This meta-analysis, though valuable, did not conduct sensitivity analyses for the quality of the studies, covered only a specific range of years and was limited to studies published in English. Therefore, the aim of this meta-analysis is: 1) to determine whether loneliness is associated with mortality, and 2) to check whether this association is the same among women and men. Additionally, this meta-analysis will be conducted with no languages and time restrictions.

Methods

Pubmed, PsycINFO, CINAHL and Scopus databases were searched for published articles that measured loneliness and mortality. The last search was run on June 27th, 2016. The following terms were used to search all articles in the databases: ((("Loneliness"[Mesh]) OR Lone*[Title/Abstract]) OR Forlorn*[Title/Abstract]) OR Desol*[Title/Abstract]) OR ("Social Isolation"[Majr] OR "Feeling isolated"[Title/Abstract]) AND ("Mortality"[MESH] OR "Death"[Mesh] OR Decease*[Title/Abstract] OR Die[Title/Abstract] OR Dead[Title/Abstract] OR Remain alive[Title/Abstract] OR Remained alive[Title/Abstract] OR "Longevity"[Mesh] OR "Survival"[Mesh]) AND (Humans[Mesh]) AND (adult[MeSH]) NOT ("Cross-Sectional Studies"[Mesh]) NOT ("Books"[Mesh]) NOT ("Validation Studies" [Publication

Type])). Search terms were tailored to each database. In addition, in order to minimize omissions, the reference sections of past reviews and meta-analysis were examined to locate articles not identified in the search.

The inclusion criteria were: articles with longitudinal observational design, prospective cohort design, meta-analysis, and systematic reviews. Articles that selected participants older than 18 years, and that used loneliness and mortality as measures of interest were included too. Articles in which mortality was the outcome measure, and loneliness was the independent variable defined as a subjective feeling that accompanies the perception that one's social needs are not being met by the quantity or especially the quality of one's social relationships, were also included.

The exclusion criteria were psychometric studies (development or validation of questionnaires or scales), articles of phase-I/II clinical trials, cross-sectional, primary prevention, ecologic, case report/case series, retrospective, and case-control studies. Non-human population, articles that did not analyze loneliness and mortality, articles that did not evaluate loneliness or perceived feelings of social isolation but other constructs such as size of the network, articles that did not consider loneliness as an independent variable, and articles that did not consider mortality as a dependent variable were also excluded. Since the aim of this study was to analyze the association of loneliness with mortality through physical disease, articles investigating death by suicide, injury, or accidents were not included. Thesis and books or book sections were excluded as well.

Three subsequent steps were performed to select the articles and collect the data. In the first step, articles with prospective and longitudinal design that addressed the effect of loneliness on mortality were identified and selected. A software package for managing bibliographies was used to eliminate duplicates. The titles and abstracts of all

the articles were checked by a researcher for inclusion or exclusion, in case the article was excluded the reason was provided. A random sample of 20% of the articles was double-checked independently by a second researcher. Initial disagreements between reviewers were solved by discussion; if no agreement could be reached a third researcher was consulted. In the second step, all included articles were fully read to confirm that they fulfilled all inclusion criteria. In the third step, objective and verifiable characteristics of each included article were extracted. In articles that presented more than one analysis, the one that adjusted by more confounders and the one that reported more causes of mortality was selected. When multiple effect sizes were reported across different levels of loneliness, the effect that was reported as "often lonely" or "severe/chronic loneliness" was extracted. Also, when effect sizes by different type of loneliness were reported, the emotional loneliness value was selected. Throughout this work the term "articles" will be used for papers found in the systematic review, while the word "studies" will be employed for papers included in the meta-analysis where the analysis and the effect sizes are provided separately for men and women or for different age groups. If there were doubts about the analyses or if the methodology was not clear, authors were contacted by e-mail.

The articles included in the meta-analysis were assessed for quality using The Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NSRI) [24]. This tool includes seven domains: 1) Bias due to confounding, 2) Bias in selection of participants, 3) Bias in measurement of interventions, 4) Bias due to departures from intended interventions, 5) Bias due to missing data, 6) Bias in measurement of outcomes (in this case mortality), and 7) Bias in selection of the reported result. Since this meta-analysis did not include articles of interventions items three, four, and five were omitted. The item related to bias due to

missing data was not considered because the dependent variable was mortality and the majority of the articles evaluated it with death registries, so they did not have missing data, and furthermore the potential bias related to the cause of death was already evaluated in item 6. Additionally, a new item that evaluated bias in the measurement of the independent variable (loneliness) was added. The response options for an overall judgment are: low risk of bias, moderate risk, serious risk, critical risk and no information. To consider an article with low risk of bias it is necessary to score in all items low risk. If at least one item was evaluated with moderate risk, the article was evaluated as presenting moderate risk of bias, the same if at least one item was considered as serious risk of bias. For bias due to confounding it was considered low risk if the article adjusted for age, sex, health status (considering chronic diseases as a possible indicator), socioeconomic status (considering education and occupation as proxy variables), smoking, and depression or anxiety; for bias in selection of participants, it was observed whether it counted with consecutive or random recruitment of participants or representative populations; for bias in measurement of mortality it was checked if the information was retrieved from a complete assessment of vital status or from a national death registry; for bias in measurement of the independent variable it was checked if the ascertainment of loneliness was done with a validated instrument; finally, it was evaluated if there was no bias in the selection of the reported result. In order to obtain complete information of the quality of the article, if it was part of a survey or referred to another article, the citations were consulted.

Statistical Analysis

The inter-rater agreement between the two researchers was estimated using the Kappa coefficient [25] with a confidence interval of the 95% and based on an analytical

method [26]. The kappa value can be interpreted as follows: <0.20, poor; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, good; and 0.81-1.00, very good [27].

From the total articles included, those reporting a survival effect were used to conduct a meta-analysis. The effect size measures used from each article included were Hazard Ratios (HRs) and 95% CIs. Articles reporting Relative Risks (RRs) were also considered and combined with those reporting HRs. If the article did not report the confidence interval, it was calculated using the standard error. For each article included, the reported effect size (HRs or RRs) was transformed to the natural logarithms. The model used to meta-analyze the articles included was based on a random effects modeling, since it provides more conservative results than a fixed effects model [28] and assumes that each sample comes from a different population and that the effects in these populations may also differ [29]. In addition, the inverse variance weighted method was used to obtain an overall effect size and 95% CI. To evaluate if the association of loneliness with mortality is the same in women and in men, a meta-analysis was conducted by gender. Moreover, as a sensitivity analysis, the magnitude of the effect of loneliness on mortality was assessed through a meta-analysis dividing articles with low or moderate risk of bias and articles with serious risk of bias.

A separate meta-analysis using the methodology described above was conducted over the articles reporting Odds Ratios (ORs) as an effect size measure, since ORs cannot be comparable with HRs or RRs [30]. .

The heterogeneity was evaluated by means of Cochran´s Q test at significant level of $p < 0.10$ [31] and quantified by the I^2 statistic, considering a substantial level of heterogeneity to be 50% or more [32]. The I^2 statistic indicates the proportion of the total variation due to that heterogeneity, while Cochran's Q measures whether the between-study variability in effect size exceeds that expected from corresponding

within-study variability. Moreover, to identify potential sources of heterogeneity and characteristics related to the association of loneliness with mortality, a random effects meta-regression was employed. The characteristics considered in this analysis were: sample size (in thousands), gender of the sample (male, female or both), publication year, follow-up duration (in years), and quality (low or moderate risk of bias vs. serious risk of bias).

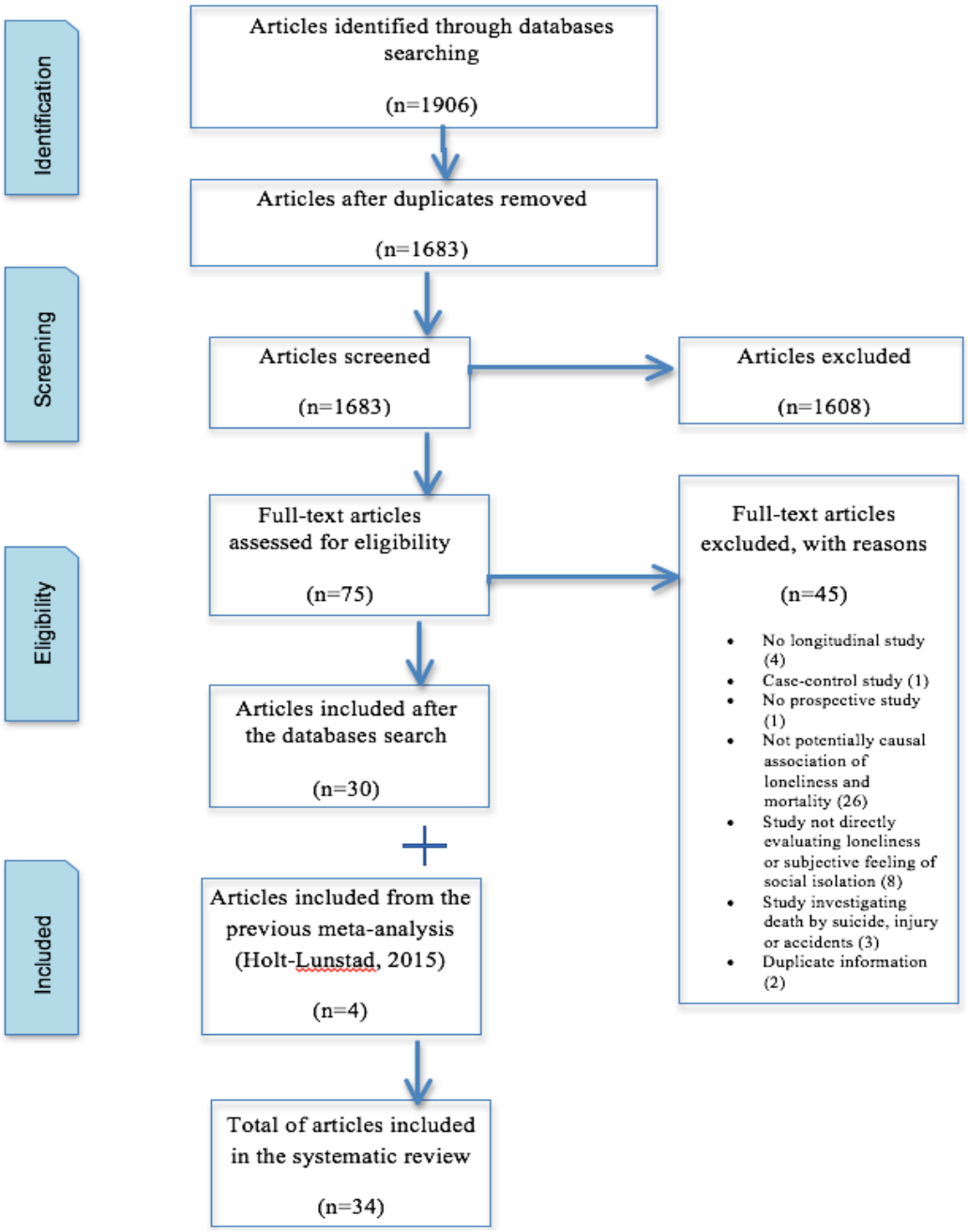
Finally, to detect publication bias, the degree of asymmetry was measured with Egger's linear regression test [33] and Begg's rank correlation test [34]. The former evaluates whether the association between estimated intervention effects and a measure of study size is greater than might be expected to occur by chance; and the latter assesses the correlation between test accuracy estimates and their variances. A funnel plot was done plotting the effect measure against the inverse of its standard error and included the fitted regression line from the Egger's test for small study effects. It was considered likely publication bias if there was an asymmetric plot and $p < 0.05$. Data analysis was performed with Stata version 11 [35] using the commands *metan, metabias* and *metareg.*

Results

All databases provided 1906 articles. The number of records was reduced to 1683 after duplicates were removed. After reading titles and abstracts, 1608 were excluded because they did not meet all inclusion criteria. A full-text review of 79 articles was carried out; 75 came from the databases and 4 (code: 5, 6, 16, 25) were found after examining the meta-analysis of Holt-Lunstad et al. [23]. In total, 34 articles were included in the systematic review. One of them was published in Spanish [36] and the

rest were written in English. Figure 1 shows the flow diagram containing the details of the articles included and excluded.

Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram.



A detailed description of the characteristics of the 34 articles included in the systematic review is reported in Table 1. From the 34 articles, a total of 42 studies were analyzed given that the articles that reported different effect sizes by gender (code: 9a, 9b, 10a, 10b, 11a, 11b, 17a, 17b, 20a, 20b, 32a, 32b) or by age group (code: 29a, 29b, 29c) were considered as different studies. The studies included in the general meta-analysis were finally 30, since 5 of them reported ORs and were meta-analyzed separately (code: 1, 5, 19, 21, 25); and 6 more did not present the effect size data needed and it was not possible to obtain it even after contacting the authors (code: 10a, 10b, 13, 15, 18, 30); and one was a meta-analysis (code: 8), whose studies are described in Table 1. Regarding the studies included in the meta-analyses, 28 were carried out in the general population (code: 3, 4, 6, 9a, 9b, 11a, 11b, 12, 14, 16, 17a, 17b, 20a, 20b, 22, 23, 24, 26, 27, 28, 29a, 29b, 29c, 31, 32a, 32b, 33, 34) and 2 analyze clinical or institutionalized population (code: 2, 7).

Table 1: Overview of studies included in the systematic review.

Code	First author	Year	Cohort (Nation)	Follow-up	Sample age	Covariates	Mortality	Results	Effect Size HR (95% CI)	General or Clinical/ institutionalized	Included in Meta-analysis
1	Cuijpers [37]	2001	424 m/f (The Netherlands)	1 Y	84.5 (mean)	Sx, Ag, YH.	All-cause (unknown)	±	* 1.06 (0.94, 1.19)	CL	no
2	Drageset [11]	2013	227 m/f (Norway)	5 Y	>65 (years)	Sx, Ag, Edu, MS, LS, CO, SI, RW, Nu, GDS.	Cancer (medical record)	±	0.96 (0.90, 1.06)	CL	yes
3	Eaker [38]	1992	749 f (USA)	20 Y	45-64 (years)	Sx, Ag, S, HS, Di, BMI	Cardiovascular disease (medical record)	+	4 (1.8, 9.2)	G	yes
4	Ellwardt [39]	2016	2911 m/f (Netherlands)	20 Y	55-85	Sx, Ag, De, CoD, ADL, An, Hs	All-cause (medical record)	±	1.02 (0.99. 1.06)	G	yes
5	Giraldi [40]	1997	95 m/f (Italy)	6Y	-70 (years)	Not controlled by covariates	Cancer (medical record)	±	* 1.93 (0.82, 4.57)	CL	no
6	Grand [41]	1990	645 m/f (France)	4Y	+60 (years)	Ag	All-cause (medical record)	±	1.42 (0.81, 2.50)	G	yes
7	Herlitz [42]	1998	1290 m/f (Sweden)	5Y	32-86 (years)	Ag, LV, S, CHF, Di, RD, PCD, IC.	Cardiovascular disease (medical record)	+	1.78 (1.17, 2,71)	CL	yes
8	Holt-Lunstad [23]	2015	Meta-analytic review (studies included in this meta-analysis were considered as separate in our meta-analysis)								no
9a	Holwerda [43]	2012	1509 m (The Netherlands)	10 Y	65-84 (years)	Ag, Edu, SIs, HD, Di, CD, Ca, ReD, Ar, Ep, Pa, De, CoD, ADL.	All-cause (medical record)	+	1.71 (1.41, 2,07)	G	yes
9b	Holwerda [43]	2012	2495 f (The Netherlands)	10 Y	65-84 (years)	Ag, Edu, SIs, HD, Di, CD, Ca, ReD, Ar, Ep, Pa, De, CoD, ADL.	All-cause (medical record)	+	1.28 (1.12, 1.46)	G	yes
10a	Iecovich [44]	2011	109 m (Israel)	18 Y	70-88 (years)	MS, NoC, FMC, NoH, SRH, CO, FS, ES.	All-cause (medical record)		Data not available	G	no
10b	Iecovich [44]	2011	115 f (Israel)	18 Y	70-88 (years)	MS, NoC, FMC, NoH, SRH, CO, FS, ES.	All-cause (medical record)		Data not available	G	no
11a	Jylhä [45]	1989	472 m (Finland)	6,5 Y	60-89 (years)	Ag, PH, FA, DD.	All-cause (medical record)	±	1.02 (0.75, 1.40)	G	yes

11b	Jylhä [45]	1989	464 f (Finland)	6,5 Y	60-89 (years)	Ag, PH, FA, DD.	All-cause (medical record)	±	1.17 (0.79, 1.74)	G	yes
12	Levy [46]	2005	620 m/f (USA)	23 Y	50-78 (years)	Sx, Ag, MS, SRH, FH, SES.	Other cause (Respiratory mortality)	±	0.28 (0.08, 1.04)	G	yes
13	Ljungquist [47]	1996	1062 m/f (Sweden)	16 Y	+67 (years)	Not controlled by covariates	All-cause (medical record)	±	Data not available	G	no
14	Luo [48]	2012	2101 m/f (USA)	6 Y	+50 (years)	Sx, Ag, Edu, MS, RFLN, SRH, Sl, PE, S, De, FL, RE, HA, HI.	All-cause (medical record)	±	1.07 (0.99, 1.17)	G	yes
15	Luo [13]	2014	14072 m/f (China)	10 Y	+65 (years)	Sx, Ag, Edu, MS, NoC, LN, UR.	All-cause (medical record)	+	Data not available	G	no
16	Maier [49]	1999	516 m/f (Germany)	7 Y	70-103 (years)	Not controlled by covariates	All-cause (medical record)	+	1.28 (1.14, 1.44)	G	yes
17a	Meller [36]	2004	82 m (Germany)	5 Y	+85 (years)	Sx, Ag, De, Cr, Ho, Ti, An, LI, RA, CRA.	All-cause (unknown)	+	1.67 (0.71, 3.87)	G	yes
17b	Meller [36]	2004	276 f (Germany)	5 Y	+85 (years)	Sx, Ag, De, Cr, Ho, Ti, An, LI, RA, CRA.	All-cause (unknown)	+	1.79 (1.03, 3.09)	G	yes
18	Miller [50]	1997	205 m (USA)	3 Y	37 (mean)	HS, CD4	Other cause AIDS-related mortality	±	Data not available	CL	no
19	Newall [51]	2013	228 m/f (Canada)	35 Y	77-96 (years)	Sx, Ag, MS, HS, Hap, IS.	All-cause (medical record)	+	* 1.21 (1.07, 1.35)	G	no
20a	Olsen [52]	1991	715 m (Denmark)	16 Y	70-100 (years)	Ag, SAH, TLH, NoH5Y, SAHC, SAMH, PM, NEH, MPA, NEEVS.	Cardiovascular disease (medical record)	+	1.70 (1.03, 2.81)	G	yes
20b	Olsen [52]	1991	1037 f (Denmark)	16 Y	70-100 (years)	Ag, SAH, TLH, NoH5Y, SAHC, SAMH, PM, NEH, MPA, NEEVS.	Cardiovascular disease (medical record)	±	1.09 (0.79, 1.49)	G	yes
21	Patterson [53]	2010	6928 m/f (USA)	34 Y	+21 (years)	Sx, Ag, Edu, MS, NoFR, PE, S, Sl, De, RE, In.	Cardiovascular disease (medical record)	±	* 1.03 (0.76, 1.39)	G	no
22	Penninx [54]	1997	2829 m/f (The Netherlands)	2,4 Y	55-85 (years)	Sx, Ag, Edu, SS, PCR, SD, PL, SRH, Al, and S.	All-cause (unknown)	+	1.06 (1.00, 1.12)	G	yes
23	Perissinotto [12]	2012	1604 m/f (USA)	6 Y	+60 (years)	Sx, Ag, Edu, RE, NWAB, Wo, LA, CO, S, Al, BMI, PE, HVP, De, ADL, UET, PM, Cl, In.	All-cause (relative record)	+	1.45 (1.11, 1.88)	G	yes

24	Pitkala [55]	2004	491 m/f (Finland)	10 Y	75, 80, 85 (years)	Sx, Ag, HS.	All-cause (medical record)	±	1.16 (0.99, 1.39)	G	yes
25	Shahtahmasebi [56]	1992	534 m/f (England)	8 Y	+65 (years)	Ag	All-cause (medical record)	±	* 1.40 (0.99, 1.99)	G	no
26	Shiovitz-Ezra [57]	2010	7638 m/f (USA)	4 Y	+50 (years)	Sx, Ag, Edu, HS, FL, De.	All-cause (medical record)	+	1.83 (1.71, 1.87)	G	yes
27	Stek [58]	2005	476 m/f (Germany)	5Y	85 (years)	Sx, Edu, MS, Ins, S, Al, CrD.	All-cause (medical record)	±	1.30 (0.80, 1.90)	G	yes
28	Steptoe [59]	2013	6500 m/f (England)	7.25 Y	+50 (years)	Sx, Ag, Edu, MS, RE, LSI, MI, Ca, Di, CHD, CLD, Ar, St, De, CES-D, We.	All-cause (medical record)	±	0.92 (0.78, 1.09)	G	yes
29a	Stessman [60]	2014	330 m/f (Israel)	20 Y	70-78 (years)	Sx, Edu, MS, PE, CP, Hy, HD, Di.	All-cause (medical record)	±	1.06 (0.54, 2.10)	G	yes
29b	Stessman [60]	2014	455 m/f (Israel)	20 Y	78-85 (years)	Sx, Edu, MS, PE, CP, Hy, HD, Di.	All-cause (medical record)	±	1.10 (0.69, 1.77)	G	yes
29c	Stessman [60]	2014	686 m/f (Israel)	20 Y	85-90 (years)	Sx, Edu, MS, PE, CP, Hy, HD, Di.	All-cause (medical record)	±	0.84 (0.56, 1.27)	G	yes
30	Sugisawa [61]	1994	2200 m/f (Japon)	3 Y	+60 (years)	Sx, Ag, Edu, MS, SC, SP, SS, SRH, CrD, FL, Al, S.	All-cause (unknown)		Data not available	G	no
31	Tilvis [14]	2011	4113 m/f (Finland)	4.75 Y	+74 (years)	Sx, Ag, SRH.	All-cause (medical record)	+	1.17 (1.02, 1.33)	G	yes
32a	Tilvis [62]	2012	1187 m (Finland)	7 Y	+75 (years)	Ag, SRH, FS, DH.	All-cause (medical record)	±	1.17 (0.97, 1.41)	G	yes
32b	Tilvis [62]	2012	2671 f (Finland)	7 Y	+75 (years)	Ag, SRH, FS, DH.	All-cause (medical record)	±	1.02 (0.89, 1.17)	G	yes
33	Tilvis [63]	2012	2490 m/f (Finland)	4.75 Y	+75 (years)	Sx, Ag, SWL, FN, PF, ZL, NFD.	All-cause (medical record)	±	1.18 (0.99, 1.42)	G	yes
34	Zhen [64]	2015	3089 m/f (China)	3 Y	+65 (years)	Sx, Ag, Edu, MS, S, RE, UR, In, PMC	All-cause (medical record)	+	1.18 (1.08, 1.25)	G	yes

Sample: Y= year (s); m= males; f= females; mf= both.
Covariates: Sx (Sex); Ag (Age); Edu (Education); MS (Marital Status); LS (length of stay in nursing home); CO (comorbidity); SI (social integration); RW (reassurance of worth); Nu (nurturance); GDS (Geriatric Depression Scale); LV (left ventricular ejection fraction); S (Smoking); CHF (congestive heart failure); Di (diabetes); RD (renal

dysfunction); PCD (previous cerebrovascular disease); IC (intermittent claudication); SIs (social isolation); HD (heart disease); CD (cerebrovascular disease); Ca (cancer); ReD (respiratory disease); Ar (arthritis); Ep (epilepsy); Pa (Parkinson); De (depression); CoD (cognitive decline); ADL (Activities Daily Life); NoC (number of children); FMC (frequency of meeting with children); NoH (number of people living in the same household); SRH (self-rated health); FS (functional status); SES (economic status); PH (perceived health); FA (functional ability); DD (disabling disease); FH (functional health); RFLN (relatives and friends living nearby); Sl (sleep); PE (physical exercise); FL (functional limitations); RE (race/ethnicity); HA (household assets); HI (household income); LN (living in nursing home); UR (urban/rural); Cr (crying); Ho (hopelessness); Ti (tiredness); An (anxiety); LI (loss of initiative); RA (repetition of acts); CRA (compulsive repetition of acts); Ne (neuroticism); PNP (proatrial natriuretic peptide); NYHAC (New York Heart Association Classification); HS (health status); Hap (happiness); IS (income satisfaction); SAH (self-assessment of health); TLH (time since last hospitalization); NoH5Y (number of hospitalizations over past 5 years); SAHC (self-assessment of health compared with others); SAMH (self-assessment of mental health); PM (physical mobility); NEH (nurse evaluation of health); MPA (mental and physical activity); NEEVS (nurse evaluation of expected vital status next year); NoFR (number of friends and relatives); In (income); SS (social support); PCR (personal coping resources); SD (specific diseases); PL (physical limitations); Al (alcohol use); NWAB (net worth of assets and debts); Wo (working status); LA (living arrangement); BMI (body mass index); HVP (hearing and vision problems); UET (upper extremities tasks); Cl (climbing); Ins (institutionalized); CrD (presence of chronic disease); LSI (long-standing illness); MI (mobility impairment); CHD (coronary heart disease); CLD (chronic lung disease); St (stroke); CES-D (Centre for Epidemiologic Studies Depression Scale); We (wealth); CP (chronic pain); Hy (hypertension); SC (social contacts); SP (social participation); SWL (satisfied with life); FN (feeling needed); PF (plans for future); ZL (zest for life); NFD (not feeling depressive); DH (daily help); RC (residential care); GOD (goes outdoors daily); CD4 (CD4 levels); PMC (covered by public medical service) .

General or Clinical/Institutionalized: G= general population; CL= clinical/institutionalized population; G/CL=both

Results: - = protective (significant); ± = null (not significant); + = harmful (significant).

Effect Size: HR= hazard ratio; RR= risk ratio; 95% CI= 95% Confidence Interval; * = effect size reported in odds ratio.

Note: The articles that reported different effect sizes by gender or by age group were considered as different studies.

Study Characteristics and Quality of the studies included in the meta-analysis

The percentage of agreement between the two independent researchers regarding whether to include or exclude each article was 98.4%, and the Kappa coefficient was 0.85 [95% CI = (0.72, 0.98)], showing a high agreement.

The characteristics of the studies included in the meta-analyses are reported in Table 2. From the 30 studies included in the meta-analysis, more than half considered both genders (63.33%), 5 analyzed only men (16.67%) and 6 analyzed only women (20.00%). The association of loneliness with mortality was evaluated in 50668 participants. A total of 11 (36.67%) studies had a follow-up longer than 10 years. Most of the studies reported all-cause mortality (80.00%) rather than a specific cause. Regarding the effect of loneliness on mortality, 56.67% reported null effect while 43.33% reported a harmful effect.

Table 2: Characteristics of the studies included in the general meta-analysis

Characteristics	n= 30
Gender: n (%)	
Both	19 (63.33)
Males	5 (16.67)
Females	6 (20.00)
Sample size: n (mean ± SE)	
Both	39011 (2053.21 ± 2116.74)
Males	3965 (793 ± 566.25)
Females	7692 (1282 ± 1041.73)
Follow-up period ≥10 Y: n (%)	11 (36.67)
Mortality: n (%)	
All-cause mortality	24 (80.00)
Cardiovascular mortality	4 (13.34)
Cancer mortality	1 (3.33)
Respiratory mortality	1 (3.33)
Effect of loneliness on mortality: n (%)	
Protective (significant)	0
Null (not significant)	17 (56.67)
Harmful (significant)	13 (43.33)

SE: Standard error; ≥10Y: Longer than ten years.

Table 3 describes the five items and the overall score that evaluates the quality of each study included in the meta-analysis according to the ACROBAT-NSRI tool of the Cochrane group. Only 2 articles (8.70%) were qualified with a low risk of bias, 9 articles obtained a moderate risk of bias (39.13%), and 12 presented a serious risk of bias (52.17%).

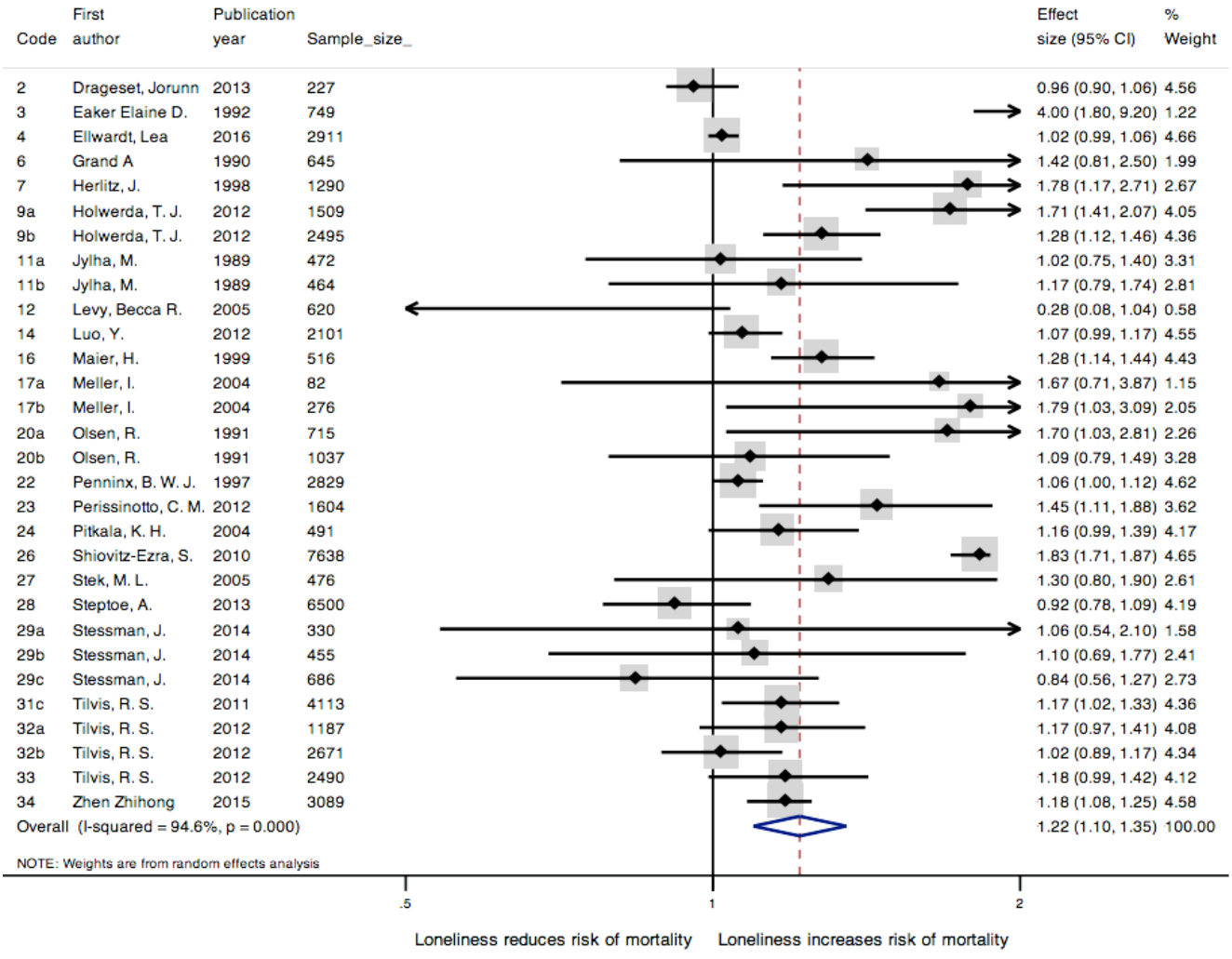
Table 3: Quality evaluation of the articles included in the meta-analysis.

Article	Bias due to confounding	Bias in selection of participants	Bias in measurement of mortality	Bias in measurement of loneliness	Bias in selection of the results	OVERALL
Drageset [11]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	**Moderate risk**
Eaker [38]	Moderate risk	Moderate risk	Serious risk	Moderate risk	Low risk	**Serious risk**
Ellwardt [39]	Moderate risk	Low risk	Low risk	Low risk	Low risk	**Moderate risk**
Grand [41]	Serious risk	Moderate risk	Serious risk	Low risk	Low risk	**Serious risk**
Herlitz [42]	Serious risk	Moderate risk	Serious risk	Low risk	Low risk	**Serious risk**
Holwerda [43]	Moderate risk	Low risk	Low risk	Low risk	Low risk	**Moderate risk**
Jylha [45]	Serious risk	Low risk	Low risk	Low risk	Moderate risk	**Serious risk**
Levy [46]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	**Moderate risk**
Luo [48]	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
Maier [49]	Serious risk	Low risk	Low risk	Low risk	Low risk	**Serious risk**
Meller [36]	Serious risk	Low risk	Low risk	Low risk	Low risk	**Serious risk**
Olsen [52]	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	**Moderate risk**
Penninx [54]	Moderate risk	Low risk	Low risk	Low risk	Low risk	**Moderate risk**
Perissinotto [12]	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
Pitkala [55]	Serious risk	Low risk	Serious risk	Moderate risk	Low risk	**Serious risk**
Shiovitz-Ezra [57]	Moderate risk	Low risk	Low risk	Low risk	Low risk	**Moderate risk**
Stek [58]	Low risk	Low risk	Serious risk	Low risk	Low risk	**Serious risk**
Steptoe [59]	Moderate risk	Low risk	Low risk	Low risk	Low risk	**Moderate risk**
Stessman [60]	Moderate risk	Low risk	Low risk	Low risk	Low risk	**Moderate risk**
Tilvis [14]	Serious risk	Low risk	Low risk	Moderate risk	Low risk	**Serious risk**
Tilvis [62]	Serious risk	Low risk	Low risk	Moderate risk	Low risk	**Serious risk**
Tilvis [63]	Serious risk	Low risk	Low risk	Moderate risk	Low risk	**Serious risk**
Zhen [64]	Moderate risk	Low risk	Serious risk	Moderate risk	Low risk	**Serious risk**

Results of the Meta-Analysis

The association of loneliness with mortality of all the studies included in the meta-analysis is reported in Figure 2. The main characteristics, the effect size, the confidence interval and the percentage of weight of each study are displayed in that figure. A box has been assigned to each study; representing the weight that the study contributed to the meta-analysis. The overall combined HRs were 1.22 (95% CI = 1.10, 1.35, $p < 0.001$), indicating a harmful effect of loneliness on mortality. In addition, a high heterogeneity between studies has been found ($I^2 = 94.6\%$), and the Cochran's Q test was significant ($\chi^2(29) = 538.75$, $p < 0.001$).

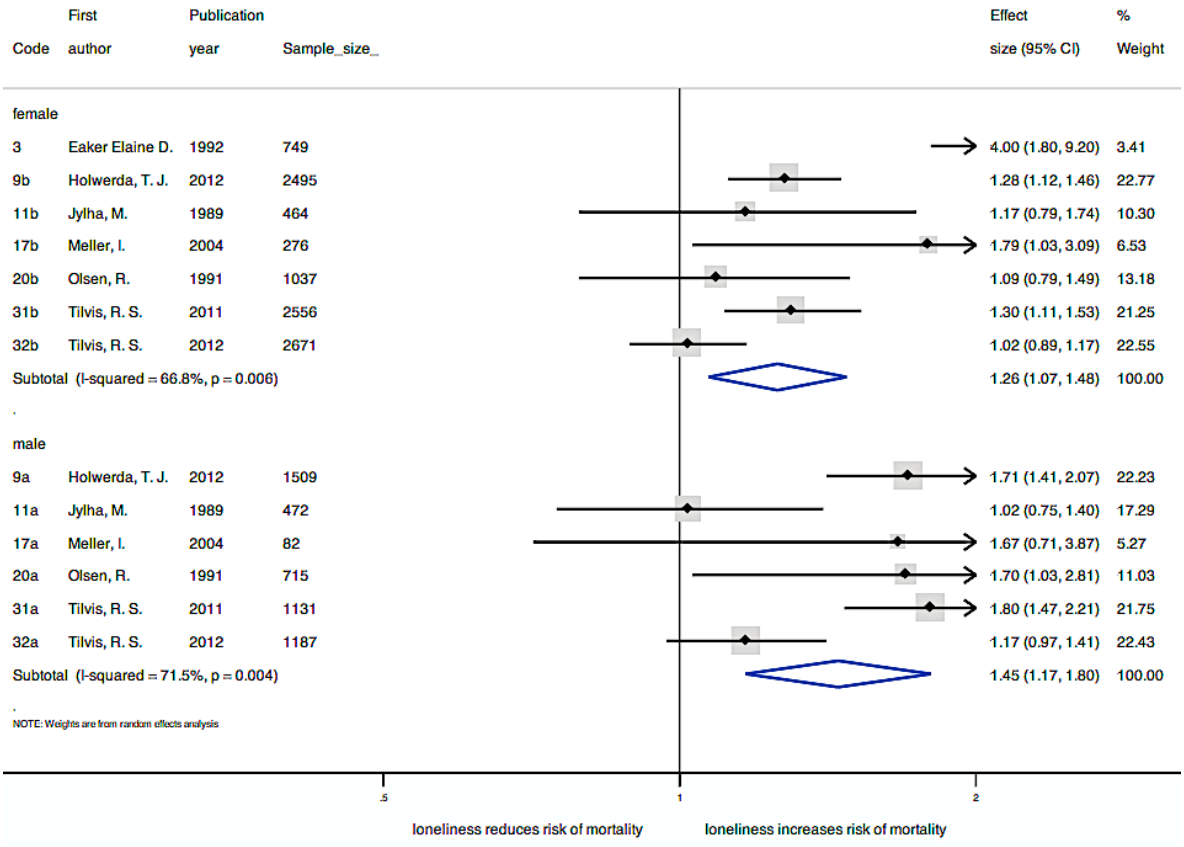
Figure 2. Forest plot of the studies included in the meta-analysis.



A similar result was obtained when a separate meta-analysis was conducted over the 5 studies reporting ORs as effect size measure (code: 1, 5, 19, 21, 25, according to the notation in Table 1). The pooled OR associated with the effect of loneliness on mortality was 1.15 [95% CI = (1.03, 1.28); p = (0.011)], indicating that loneliness was a risk factor for mortality. In this case, the Cochran's Q test was not significant ($\chi^2(4)$ = 5.68, p = 0.23) and the level of heterogeneity was moderate (I^2 = 29.5%).

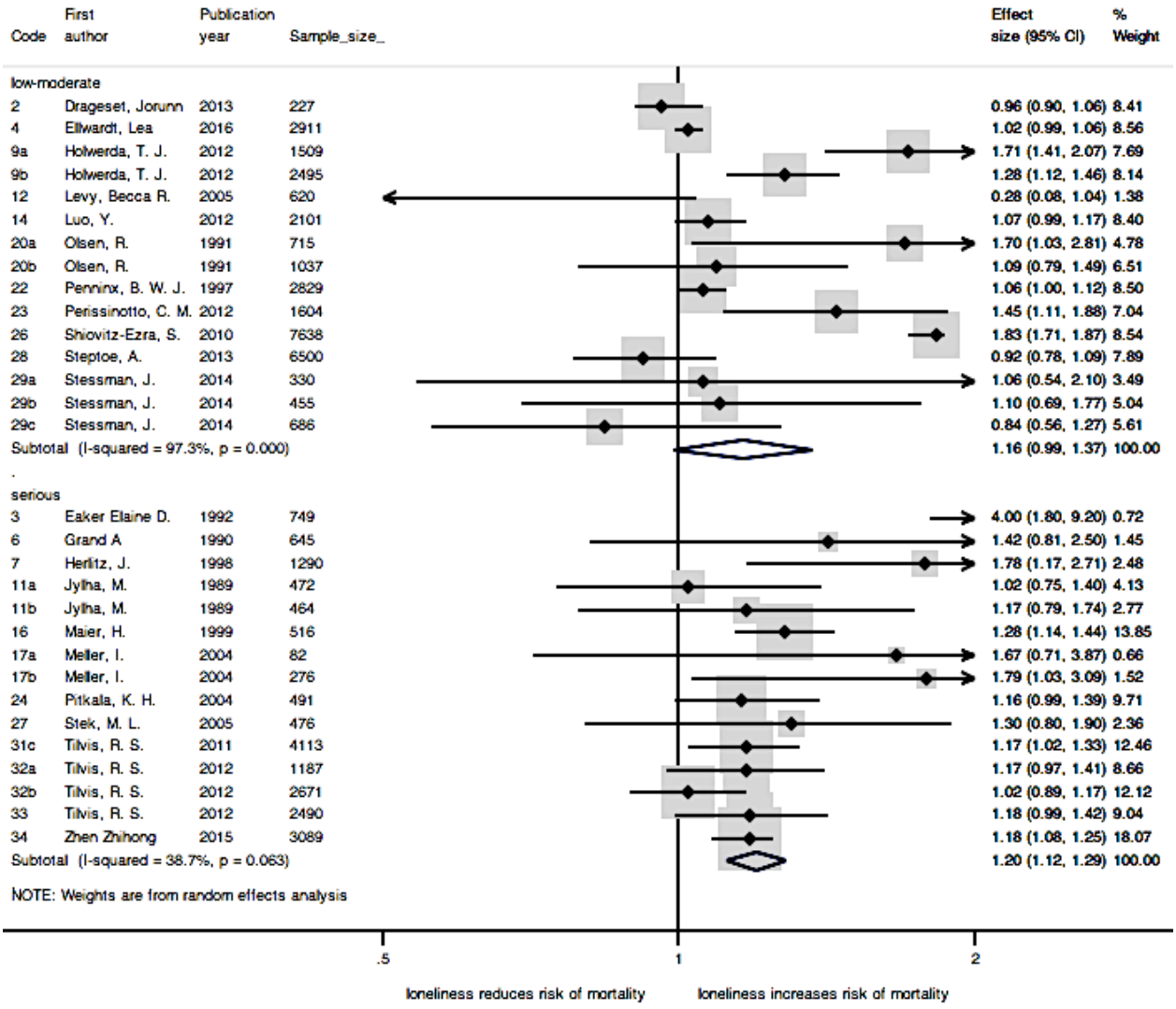
In reference to the meta-analysis carried out by gender (Figure 3), the overall HRs were 1.26 (95% CI = 1.07, 1.48, p = 0.005) for women and 1.45 (95% CI = 1.17, 1.80, p = 0.001) for men. In both groups loneliness was a risk factor for mortality. The heterogeneity was high in both subgroups: I^2 = 66.8% and a significant Cochran's Q test ($\chi^2(6)$ = 18.06, p = 0.006) for women, and I^2 = 71.5% and a significant Cochran's Q test ($\chi^2(5)$ = 17.56, p = 0.004) for men.

Figure 3. Forest plot of the studies included in the meta-analysis by gender.



Considering the risk of bias of the studies, low and moderate risk versus serious risk, the effect of loneliness on mortality remained null, although it indicated a trend towards a significant risk factor (HR = 1.16; 95% CI = 0.99, 1.37, $p = 0.070$), for the studies with low and moderate risk, while in the studies with serious risk of bias loneliness was a risk factor (HR = 1.20; 95% CI = 1.12, 1.29, $p < 0.001$). The Cochran's Q test was χ^2 (14) = 515.85, $p < 0.001$ for low and moderate risk and χ^2 (14) = 22.83, $p = 0.063$ for serious risk, I^2 values were 97.3% and 38.7% respectively (Figure 4).

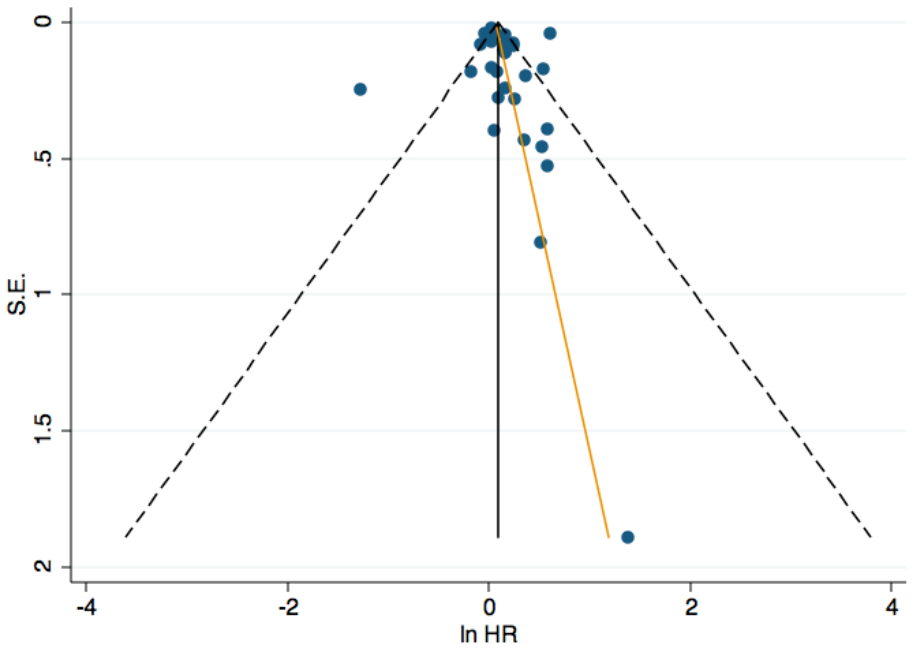
Figure 4. Forest plot of the studies included according to the risk of bias.



In order to explore potential causes of heterogeneity and to analyze significant characteristics of the studies associated with the effect sizes obtained, a meta-regression was carried out. The results showed that the years of follow-up was the only variable that influenced significantly in the association of loneliness and mortality [coef. = -0.022, 95% CI = (-0.043, -0.001); $p = 0.042$].

Based on the 30 studies included in the general analysis, potential publication bias was assessed. The publication bias is illustrated in Fig 5, where Begg's rank correlation test indicated no publication bias ($p = 0.36$), as well as Egger's linear regression: the estimated intercept for the fitted regression model was 0.60 with a standard error of 0.74, giving a p-value of 0.43. In Figure 5, the funnel plot appears symmetric with a distribution of the effect sizes mainly in the top and in the right side of the graph, suggesting no publication bias.

Figure 5. Funnel plot depicting the relationship between effect size and standard error of effect for the studies in the meta-analysis.



Discussion

The overall meta-analysis shows that loneliness has a trend to be associated with mortality. This outcome is consistent with a recently published meta-analysis that also analyzes the association of loneliness with mortality [23]. However, when the studies were separately analyzed by quality, studies with serious risk of bias reported an association between loneliness and early mortality while in studies with low and moderate risk of bias loneliness had a null effect. In view of these results, it seems that loneliness has a marginal association with mortality but when the studies control for a higher number of covariates especially health or comorbidity variables, the effect of loneliness on mortality disappears. According to the findings of Sugisawa et al. [61], loneliness could have an indirect effect on mortality through chronic diseases, functional status and self-rated health. Luo et al. [48] explain that social relationships, health behaviors, and health outcomes could be considered as potential mechanisms through which loneliness leads to increases in mortality risk.

In the meta-analysis by gender, loneliness shows a tendency to be associated with mortality both in men and women. However, this effect was slightly higher in men than in women. An explanation of this difference could be that men are more reluctant to admit feelings of loneliness than women for cultural reasons [16]. Consequently, it might be that men report loneliness when its severity is high and consequently its impact is stronger. Moreover, women tend to associate loneliness with an evaluation of their overall network or relationships whereas men tend to associate this feeling with an evaluation of the relationship with their partner [19], and during the aging process the probabilities of becoming a widow increase, which might contribute to loneliness. Furthermore, widowhood has more adverse effects in men than in women and this might be because when men become widowed they have to readapt to new roles that

could represent difficulties for them, like domestic tasks and assisting children [65]. The association of loneliness with health [9, 66, 67] and the fact that men generally have more negative attitudes towards care seeking [68] may also be implicated in this relationship. In addition, previous articles have shown that lonely men are more likely to suffer lower life satisfaction and higher depression, and are less resilient than lonely women [69]. In this line, some authors have suggested that the impact of social isolation on mortality might be greater in men because they experience increased inflammatory responses when they are alone than women [70]. Moreover, unhealthy lifestyles (i.e. tobacco and alcohol problems) have been associated with loneliness [71], and also more frequent in men [21], which could also explain the stronger loneliness-mortality connection in men than in women. However, the interaction of environmental and biological factors and their role needs to be further explored.

The strengths of this work include its high sensitive search that covered all years and languages, and the inclusion of a revision of references of previous reviews and meta-analyses related to the topic of interest. Moreover, this meta-analysis updates the data regarding the association of loneliness with mortality and includes a higher number of articles and a higher number of participants compared with the previous meta-analysis. Additionally, an evaluation of the quality of each included article was done in order to analyze if the association of loneliness with mortality differs according to the quality of the studies. Furthermore, good agreement between the reviewers who did the double-check of the articles was found. To our knowledge, this is the first meta-analysis that evaluates this association of loneliness with mortality in both genders independently.

A number of limitations should be born in mind when interpreting the results. First, even though the included articles are longitudinal, causality cannot be inferred

since all of them are observational. Second, only articles published in peer-reviewed journals were included, "grey literature" was excluded, which may have limited the findings. Third, half of the studies included in this meta-analysis were qualified as having serious risk of bias, which indicates that cautions must be taken when interpreting the results. Fourth, high levels of heterogeneity, mainly in the analysis of low-moderate risk of bias studies, were obtained. Some reasons that might explain this high heterogeneity are: a high diversity of instruments used to measure loneliness, a large variety of covariates used in each study to control their effect in the association between loneliness and mortality, the wide range of publication year, the age differences analyzed in each study, and the contrast between the sample sizes. Fifth, in some cases it was not possible to obtain the necessary information to include some studies in the meta-analysis (e.g. standard deviation, confidence intervals, a measure of the effect size of loneliness, the sample size, or a comparable effect size value) even after contacting the authors.

Despite these limitations, some conclusions can be drawn from this article. Loneliness shows a trend to be a risk for mortality and this effect is slightly stronger in men than in women, but this trend disappears when the studies control by health status or comorbidities. Therefore, it seems that health has a moderating relationship between loneliness and mortality given that after controlling for health covariates the effect of loneliness on mortality disappear. Furthermore, it is evident that there is a need for more studies that analyze the mediating role of health conditions in the relationship between loneliness and mortality, and that analyze whether health conditions also impact on the level of loneliness. In addition, qualitative studies that help to understand the differential experience and the possible related factors to loneliness in men and women,

articles that use validated questionnaires for loneliness, and articles that control by health confounders, are also needed.

Further studies should evaluate the association of loneliness with mortality across age, especially in the young population. Only five articles analyzed in this study had a sample younger than 50 years [38, 40, 42, 50, 53]. Besides, more articles with clinical or institutionalized population are needed since only two studies [11, 42] of those included in the meta-analysis performed analyses with this population.

Understanding the differential impact of loneliness in women and men is crucial to develop a better understanding of the nature of these feelings and approach the circumstances of the risk group. More research with low risk of bias is required to clarify and fully explore the possible association of loneliness with mortality and to suggest future recommendations in relation to prevention and treatment.

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6. RESULTS

In this chapter a summary of the main findings of the three studies included in this thesis is presented. The results are described in detail in the previous chapter.

6.1. The results obtained regarding the association of loneliness and the components of the social network with health were:

- Finland showed lower prevalence of loneliness than Poland and Spain.
- Regarding social networks, the size of the network was bigger in Finland and Spain, whereas the quality of the network was better in Poland than in Finland and Spain.
- There were statistically significant differences in quality of the network, frequency of contact with the members of the network, and loneliness in the younger group (people aged 18–49), whereas in the older group (participants older than 50 years) significant differences were found in loneliness, size and quality of the network, and frequency of contact.
- Regarding health status, Finland was the country with best health status, whereas Poland had the worst health status.
- The mean score of loneliness was higher in women than in men, and a trend of higher scores was observed in older population as compared to the younger one.
- Quality of the network and frequency of contact with the members of the network were highly related, whereas loneliness and size of the network, and loneliness and quality of the network were moderately related.

- Loneliness added a significant increase in the percentage of variance explained in the model, but the components of the social network did not. This result was similar in Finland, Poland and Spain.

- A higher age, presence of depression and a higher score on loneliness were associated with a worse health status.

- Loneliness was associated with health, and this association was stronger in Finland than in Poland and Spain.

- The frequency of contact with members of the network was significantly associated with better health whereas the quality and the size of the network were not significantly associated.

- Men had a better health status than women.

- The relationship between frequency of contact with members of the network and health was slightly stronger in Poland than in Finland and Spain.

- When age increased, the relationship between loneliness and health was less strong.

- The relationship of loneliness with health did not change by gender.

6.2. The results obtained regarding the relationship between social isolation and loneliness with the use of healthcare services are:

- Before the baseline interview, a total of 21.3% of participants frequently used outpatient care and 21.7% had been hospitalized in the 12 months, whereas before the follow-up interview. 19.6% had frequent outpatient care use and 11% had been hospitalized in the 12 months.

- A total of 1,353 (56.1%) respondents did not participate in organizations, social clubs or groups, religious services or committees, whereas 163 (6.8%) participants had less than monthly contact with family.

- Based on gender mean scores, significant differences were found in frequent outpatient care use, comorbidities, presence of limitations in Activities of Daily Living (ADLs), limitations in Instrumental Activities of Daily Living (IADLs), employment, the Social Isolation Index and its components (e.g. being unmarried, having less than monthly contact with children, with friends and no participation), years of education, and loneliness.

- Loneliness was significantly associated with frequent outpatient care use in women but not in men, after controlling for socio-demographic variables and comorbidities.

- Regarding social isolation, when it was analyzed as a dichotomous variable, it was not associated with frequent outpatient care use after controlling for potential confounders in women or in men. Nevertheless, when the components of the Social Isolation Index were analyzed separately, being unmarried and

having less than monthly contact with other family members were associated with frequent outpatient care use in women but not in men.

- Social isolation and loneliness were not associated with inpatient care use.

6.3. The results obtained regarding the meta-analysis that studied the gender differences of the association of loneliness with mortality are:

- A total of 34 articles that analyzed the impact of loneliness on mortality were found.

- Regarding the studies included in the meta-analyses, 28 (93.33%) were carried out in the general population and 2 analyzed clinical or institutionalized population. More than half of the studies considered both genders (63.33%), 5 analyzed only men (16.67%) and 6 analyzed only women (20.00%).

- The association of loneliness with mortality was evaluated in 50,668 participants. A total of 11 studies (36.67%) had a follow-up longer than 10 years. Most of the studies reported all-cause mortality (80.0%) rather than a specific cause of death.

- In relation to the effect of loneliness on mortality, 56.67% reported null effect whereas 43.33% reported a harmful effect.

- When the quality of the articles included in the meta-analysis was evaluated, according to the ACROBAT-NSRI tool, 2 articles (8.70%) were qualified with a

low risk of bias, 9 articles obtained a moderate risk of bias (39.13%), and 12 presented a serious risk of bias (52.17%).

- The results of the meta-analysis indicate a harmful effect of loneliness on mortality, with an overall combined HR of 1.22 (95% CI = 1.10, 1.35, $p < 0.001$), and a high heterogeneity between studies.

- In reference to the meta-analysis carried out by gender, the overall HRs were 1.26 (95% CI = 1.07, 1.48, $p = 0.005$) for women and 1.45 (95% CI = 1.17, 1.80, $p = 0.001$) for men. In both groups loneliness was a risk factor for mortality, and the heterogeneity was high in both subgroups.

- In addition, a meta-analysis was also done considering the risk of bias of the studies, low and moderate risk versus serious risk. For the studies with low and moderate risk, the effect of loneliness on mortality remained null, although it indicated a trend towards a significant risk factor (HR = 1.16; 95% CI = 0.99, 1.37, $p = 0.070$). On the other hand, in the studies with serious risk of bias loneliness was a risk factor (HR = 1.20; 95% CI = 1.12, 1.29, $p < 0.001$).

- The analysis that explored potential causes of heterogeneity and analyzed significant characteristics of the studies associated with the effect sizes, showed that years of follow-up was the only variable that significantly influenced the association of loneliness and mortality.

7. DISCUSSION

The results of the three studies that comprise this thesis show that loneliness and social networks have implications on different aspects of health. In the first study, it was observed that loneliness had a significant association with a worse health status. In relation to the social network, the frequency of contact with the members of the network was associated with better health status, whereas the quality of the contact and the size of the network were not. In the second study, it was found that loneliness and two items from the Social Isolation Index: being unmarried and having less than monthly contact with other family members, were associated with a frequent use of outpatient healthcare in women. Finally, the third study showed that loneliness had a trend to be associated with mortality. This trend was slightly higher in men than in women. The main findings of the three studies are briefly summarized in the Figure I.

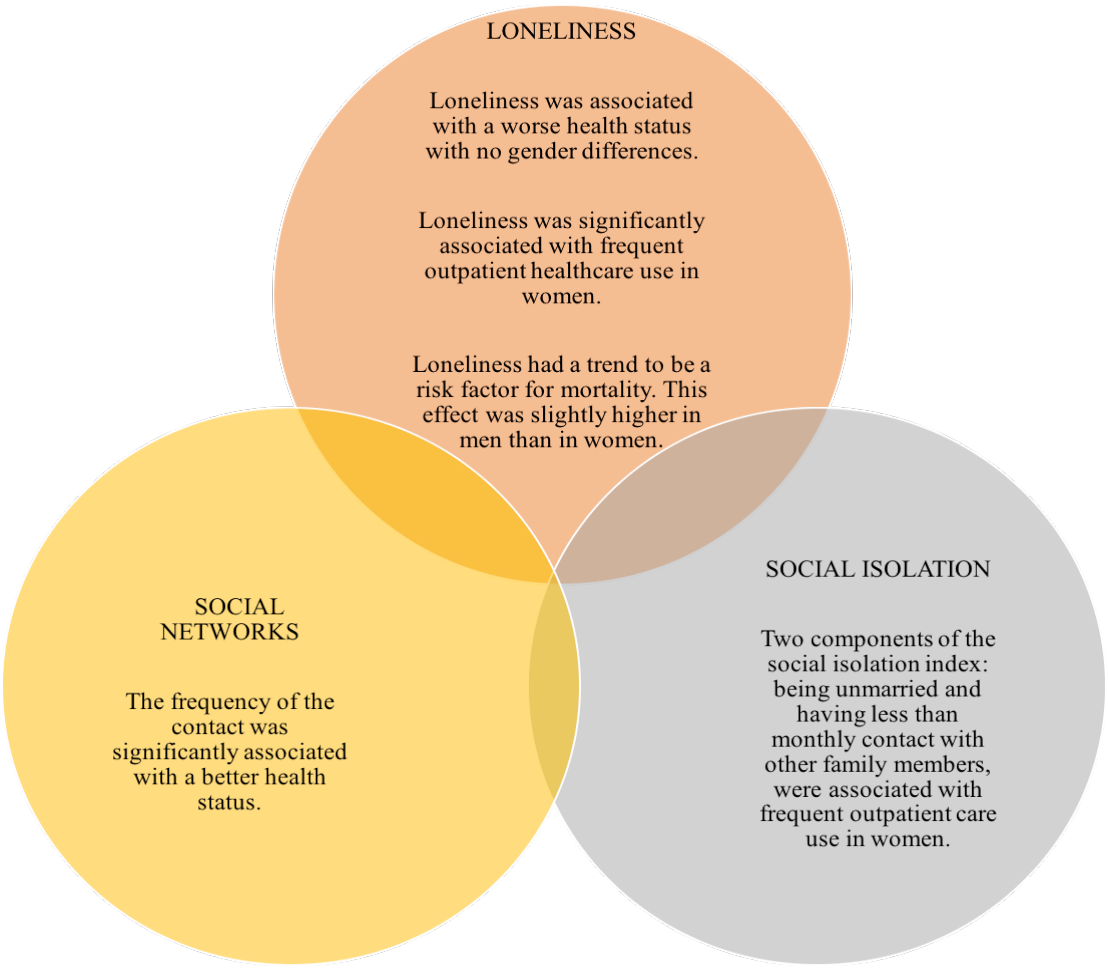

Figure I. Main findings of the three studies included in the present thesis

This thesis meets the objective of shedding light on the adverse effects of loneliness on different aspects of health. Social isolation and the components of the social network also had a relationship with health aspects. Nevertheless, these relationships were not as strong as the ones with loneliness. For this reason, this first part of the discussion focuses mainly on the loneliness mechanisms.

It is interesting to observe that loneliness had a strong association with health, but with mortality it had only a trend. The meta-analysis included in this thesis showed that in the studies belonging to the high risk of bias group, loneliness was a statistically significant risk factor for mortality, whereas in the group of studies with low risk of bias (mainly because they controlled for health problems, comorbidities or health status), loneliness has a null effect on mortality. It could be interpreted that the pathway through which loneliness is related to mortality includes health status, and in the middle of this pathway is the use of healthcare services. In other words, loneliness is associated with a worse health status. Moreover, greater loneliness is related with a frequent use of healthcare services, either because these people have worse health, or because they look for a social contact or social support. If loneliness is not treated and health status worsens, the risk of mortality may increase substantially. The mechanism of action of loneliness is the topic to which I will turn in the following paragraphs.

According to the model developed by Cacioppo et al. (2006), when someone experience feelings of loneliness, she or he feels unhappy, unsafe and activates anachronistic survival mechanisms that increase the sensibility to threats and attacks from all sides. In consequence, loneliness activates a constellation of socioemotional processes. These individuals are hyper vigilant and set off defensive behaviors to prevent rejections, treachery, and attacks from others, which may reduce the negative interactions but at the cost of presenting anxiety, hostility, low social support, low self-

esteem and blaming. In this line, negative social expectations tend to provoke rejection behaviors from the environment, which confirms lonely person´s expectations. Lonely people actively distance themselves from possible social partners even though they believe that the reason of the social distance is attributable to others and it is out of their control (Hawkley and Cacioppo, 2010). Moreover, there are negative consequences of loneliness given the hypervigilance and the decrease in self-regulation that lead to impairments in attention, cognition, affect, and behavior, which have implications on mobility through their effect on genetic, neural, and hormonal mechanisms (Cacioppo and Cacioppo, 2014; Hawkley and Cacioppo, 2010).

Some studies suggest that there is a possibility that loneliness might be heritable (Boomsma, Willemsen, Dolan, Hawkley, and Cacioppo, 2005; Cole, 2008; Hawkley and Cacioppo, 2010; McGuire and Clifford, 2000). Loneliness and social isolation are associated with an increased risk of inflammatory diseases, given the impaired glucocorticoid receptor-mediated signal transduction. More concretely, there is a problem of the cellular genome to "hear" the anti-inflammatory signal sent by circulating glucocorticoids, which makes that the inflammatory processes continue relatively out of control (Hawkley and Cacioppo, 2010). In order to study neuroendocrine-immune dynamics and social factors, Cole (2008) carried out a study based on biomarker analysis. In this article, it was found that loneliness and social isolation may alter immune cell sensitivity to physiologic regulation by the hypothalamic-pituitary-adrenal (HPA) axis, even after controlling for different biological, social, behavioral, and psychological cofounders. The effect on HPA may contribute to the increased physical health risks and alterations of gene expression. The HPA axis mediates physiologic stress reactions from a variety of other non-inflammatory challenges (for example, psychological or social stressors), and the

competing functional demands have the possibility of undermining the optimal control of inflammatory gene expression (Cole, 2008). A study that examined 8,387 adult twins found that the estimate of genetic contributions to individual differences in feelings of loneliness was 48% (Boomsma, Willemsen, Dolan, Hawkley, and Cacioppo, 2005). These results showed no evidence of a change in heritability when the sample was divided into young adults and older adults or by gender. In addition, a study carried out with 275 pairs of child siblings (monozygotic and dizygotic) revealed significant heritability and non-shared environmental influences on feelings of loneliness (McGuire and Clifford, 2000). It is important to keep in mind that having a gene or genes associated to loneliness does not necessary mean that the person will be lonely, environmental circumstances that evocate distress by social disconnection are needed. Some factors negatively related to distress are: the social network size, satisfaction and frequent contact with the social network, and having a spousal confidant (Hawkley et al., 2008).

The distinction between loneliness, social isolation and social network is necessary in order to have a better understanding of these phenomena, and to properly treat them. Loneliness is not simply being alone and it is not synonymous with objective social isolation (Hawkley and Cacioppo, 2010). In this line, the quality of the relationships is relevant for the social nature of the human species. Humans require not only the presence of others, but the presence of others who value us, whom we can trust, communicate with, collaborate together with to survive, reproduce with, care of our offspring with and to continue with the lineage (Cacioppo and Patrick, 2008).

7.1. Loneliness, social networks, and health

The only component of the social network significantly associated with health was the frequency of contact with the members of the network. This association was slightly stronger in Poland than in Finland and Spain, although all the differences between the three countries were small. Similarly, another article that analyzed social relationships in Spanish elderly found that the frequency of social interactions was highly associated with health (Fernández–Ballesteros, 2002). Regarding loneliness, the results show that after controlling for relevant covariates, it was strongly related to health in Finland, Poland and Spain. This is consistent with other studies that have also evaluated loneliness with the UCLA Loneliness Scale (Cacioppo et al., 2002; Cacioppo et al., 2010; Pressman et al., 2005). The differences across countries were slight. However they are in line with previous research that also found differences among countries (Sundström et al., 2009). According to the model of Hawkley and Cacioppo (2010), loneliness has effects on health, mainly by contributing to morbidity and mortality.

The results support the hypothesis that postulated that a stronger association would be observed between loneliness and health than between the components of the social networks and health. Loneliness was associated more with health than the three components of the network. Other studies have also confirmed this finding (Stephens, Alpass, Towers, and Stevenson, 2011; Steptoe et al., 2013). In the research of Stephens et al. (2011) that analyzed the effect of social networks on health in a representative sample from New Zealand, it was found that loneliness contributed more to health aspects than any aspect of the social network. Furthermore, another study showed that loneliness was related to a greater range of health conditions than social isolation, some

of them were coronary heart disease, stroke, and clinical depression. However, when the authors focused on mortality, social isolation remained significant but loneliness did not. They suggested that the strong association between loneliness and baseline health could explain this result (Steptoe et al., 2013).

7.2. Social isolation, loneliness and use of healthcare services

The main aim of the second study was to evaluate whether social isolation and loneliness are prospectively associated with healthcare services use, and to assess whether these associations differed by gender. According to the results, loneliness and two items of the Social Isolation Index, being unmarried and having less than monthly contact with other family members or not having other family members, were longitudinally related with frequent outpatient care use in women. For inpatient care use, neither loneliness nor social isolation had a significant association in women or men.

Gender differences regarding the association of loneliness and the use of outpatient care services were found. This association was significant in women but not in men. The frequent use of outpatient care in lonely people could be due to the perception of the physician as a familiar person with whom one can talk (Cheng, 1992), interact, or have an interpersonal stimulation (Gerst-Emerson and Jayawardhana, 2015). In relation to the social isolation, there was not a significant association with frequent outpatient care use in men. However, regarding women, two items were associated with frequent outpatient care use: being married and having less than monthly contact with other family members. These findings are not consistent with previous studies that

showed that social isolation was not related with a high use of medical services (Iliffe et al., 2007; Lasebikan, Owoaje, and Asuzu, 2012). Nevertheless, these studies did not disentangle the components of social isolation to observe the association of each component with healthcare use; instead, they focused on a global score. Additionally, the organization of the healthcare system, as well as the prevalence of loneliness and social isolation may be different in each country. The national healthcare system of Spain is mainly funded by general taxes. This system covers primary and specialized care, but a few services, such as dental care, are not included (Garrido-Cumbrera et al., 2010). Regarding gender, it may be that differing lifestyles, as well as life situations in men and women, explain the differences found in the relationship of loneliness and social isolation with healthcare use. Women live longer and they tend to marry men older than themselves (Lennartsson and Lundberg, 2007). This situation may lead women to become widowed earlier and they might look for social support and contact in the healthcare services. In this line, Oliver, Pearson, Coe, and Gunnell (2005) found that being a women was a factor associated with help-seeing. These authors suggest that both a weak social support and having few social contacts may explain a high frequency of visits to the primary care physician.

Most of the studies that analyzed healthcare use only focus on loneliness or social isolation, but none have analyzed both simultaneously. The research carried out on loneliness found that lonely people visit health services frequently (Cheng, 1992; Ellaway et al., 1999; Hall and Havens, 1999; Newall, McArthur, and Menec, 2015). On the other hand, when social isolation is analyzed some articles show a frequent use of health services (Ellaway et al., 1999; Longman et al., 2012) and others do not find this trend (Iliffe et al., 2007; Lasebikan et al., 2012). A possible reason for the different findings regarding loneliness and social isolation could be that a lonely person would

like to improve his or her social network and social support through contacts with professionals of the healthcare system, whereas an isolated person could feel comfortable and not try to increase his or her network.

Finally, there was no significant association between loneliness and social isolation with inpatient care use. An explanation could be that the visits to the physician depend on the patient while hospitalization is a decision made by the physician. Moreover, the relationship developed with an outpatient care physician might be stronger because they are usually seen more frequently than inpatient care professionals (Gerst-Emerson and Jayawardhana, 2015).

7.3. Loneliness and mortality, gender differences

According to the findings of the third study, loneliness had a trend to be related with mortality. In the analysis carried out that included all of the studies, loneliness had a harmful effect on mortality. Nevertheless, when the sample was divided into groups with different risk of bias (low and moderate risk versus serious risk), loneliness showed a null effect for the group with low and moderate risk, whereas it was a risk factor for the serious risk group. Furthermore, when the studies controlled for a higher number of covariates, this association was no longer significant. A previous study suggested that loneliness may have an indirect association with mortality through chronic disease, functional status, and self-rated health (Sugisawa, Liang, and Liu, 1994). Also, Luo et al. (2012) suggested that social relationships, health behaviors, and health outcomes may be potential mechanisms through which loneliness increases the risk of mortality.

The meta-analysis done by gender showed that loneliness had a tendency to be a risk factor for mortality in both groups, but slightly higher in men than in women. One reason might be that in light of cultural aspects, women tend to more easily admit their feelings of loneliness than men (Dahlberg et al., 2015). Hence, it could be that men acknowledge being lonely when both the severity and the impact of these feelings are high. Furthermore, women associate loneliness with their entire networks, whereas men are more prone to associate loneliness with the presence of their partner. During the elderly period, the association of loneliness with having a partner might contribute to feel lonely given the strong possibility of becoming widow (Tijhuis et al., 1999). In addition, widowhood may affect men more than women due to the difficulties they might have adapting to the new roles, such as domestic tasks and assisting members of the family (Lee, DeMaris, Bavin, and Sullivan, 2001). Another important point to take into consideration is the strong relation of loneliness with health (Hawkley, Preacher, and Cacioppo, 2010; Hawkley, Thisted, Masi, and Cacioppo, 2010; Wilson et al., 2007) and the negative attitudes that men sometimes have towards attending healthcare services (Buffel, Van de Velde, and Bracke, 2014). Previous studies also found that lower life satisfaction, higher depressive symptoms and less resilience were more common in lonely men than in lonely women (Zebhauser et al., 2014). Yang, McClintock, Kozloski, and Li (2013) explain that the impact of social isolation on mortality is stronger in men since they experience higher inflammatory responses than women. Another way to understand gender differences in relation to the impact of loneliness with mortality is that unhealthy life styles associated with loneliness, like tobacco and alcohol consumption (Stickley et al., 2013), are more frequent in men than in women (Mendis, 2014). Nevertheless, it is also relevant to keep in mind the interaction of environmental and biological factors, which needs to be further explored.

7.4. Strengths and limitations

This thesis comprises three studies that add knowledge to the field of loneliness, social networks, social isolation, and different health aspects. Moreover, the studies are pioneers in analyzing loneliness and social components together and at the same time disentangling its components to observe the different associations with health aspects. One of the empirical studies analyzed samples from different European regions in order to compare these associations between countries with diverse socio-economic and health characteristics, and welfare systems. Furthermore, the questions and the instruments used to evaluate loneliness, social isolation and the different components of the social networks have been employed in previous studies that also focus on social aspects. The UCLA loneliness scale is a validated questionnaire (Hughes, Waite, Hawkley, and Cacioppo, 2004) that can be completed in few minutes, and it is frequently used in large population surveys (Pikhartova, Bowling, and Victor, 2014; Shankar, Rafnsson, and Steptoe, 2015). In the three studies, gender aspects were taken into consideration, since previous studies showed that social aspects are different for men and women.

Other strengths of this thesis are that two of the studies were carried out with national representative samples, and one of them is a longitudinal study that allows for observing associations over time. In this line, the response rates of the survey *COURAGE In Europe-Edad con Salud* are adequate. Even though there are not strict standards, surveys carried out with general European populations obtained similar percentages to the ones obtained in this survey, such as SHARE (global response rate of 61.8%) (Börsch-Supan, Hank, and Jürges, 2005), ELSA (response rate of 67%) (Marmot, Banks, Blundell, Lessof, and Nazroo, 2002) and TILDA (response rate of 62%) (Whelan and Savva, 2013). Although Finland had the lowest score in comparison

to Spain and Poland, this is congruent with a global decrease in the response rate of many international epidemiological studies (Morton, Cahill, and Hartge, 2006). For example, in the NordChild 2011 survey, Finland had a response rate of 48.06%, as well as other Nordic countries like Iceland (47.5%), Norway (49.4%), and Sweden (45.7%) (Hohwu et al., 2013).

Regarding the meta-analysis, a highly sensitive search that considered all years, all languages, and references from previous meta-analysis and systematic reviews was carried out, resulting in a higher number of articles and participants in comparison with previous meta-analyses in the field. All these strengths make this study, to the best of my knowledge, one of the most comprehensive in the field of loneliness and mortality. In this line, no other meta-analysis analyzed the association of loneliness with mortality by groups with different risk of bias.

Nevertheless, it is important to interpret the findings of this thesis with caution given that a number of limitations should be taken into consideration. The results obtained from this thesis are based on self-reports. Self-reported information may introduce uncertainty about subjective interpretation of the questions, influenced by the respondents' understanding, experiences, expectations and culture. Besides, the design of the studies does not allow for establishing causality from the associations. In the two empirical studies, some participants were excluded for different reasons: a) they did not answer some questions about loneliness, social networks, social isolation, health status, or healthcare services use, and therefore had missing data; b) they were cognitively impaired and instead a proxy was asked some questions about the health of the participant but not about his/her social networks, loneliness, and social isolation; c) they ended the interview before answering the questions about loneliness, social networks,

social isolation, health status, and healthcare services use. Institutionalized populations were not included.

Some limitations of this thesis are specific of the meta-analysis. This study was limited to the inclusion of only articles published in peer-reviewed journals. Therefore, "grey literature" was not included. The results of this meta-analysis should be interpreted with caution because half of the studies included in the analyses were evaluated with a serious risk of bias. Moreover, high levels of heterogeneity were observed. This could be because of the broad diversity of instruments used to evaluate loneliness, the large variety of covariates used in the included studies, the wide range of publication year, the different age groups analyzed in each study, and the contrast between the sample sizes. Finally, some studies could not be included in the meta-analysis given that necessary information was not obtained even after contacting the authors.

In general terms, it can be observed that in spite of the limitations of the three studies, this thesis demonstrates the high importance of loneliness, social networks, and social isolation for different health aspects given their effects and significant associations.

7.5. Implications and future directions

Some implications and recommendations can be established from the results of this thesis. Social networks, social isolation and loneliness are important aspects for public health. In order to reduce healthcare use and provide adequate attention to the patients, it is necessary to train health professionals to identify patients' social needs,

intervene among those who are lonely or isolated and refer them to the adequate service. Screening, evaluating, and treating the feeling of loneliness, social isolation and the different components of the social network in people with poor health status and who frequently use outpatient care, is advisable. In this line, from the clinical and research perspective, it is essential to identify, analyze, and treat the social aspects separately not as interchangeable concepts since they can be experienced independently (i.e. an isolated person may not necessary feel lonely) (Matthews et al., 2016). Previous studies also support the idea of considering these social aspects independently, mainly loneliness and social isolation (Coyle and Dugan, 2012) given that they are different concepts (Masi, Chen, Hawkley, and Cacioppo, 2011).

Suggestions for future lines and studies can be made according to the results obtained. It seems necessary to carry out longitudinal studies that focus on the association of loneliness and the components of the social networks with health in order to be able to analyze trajectories. Moreover, research carried out with institutionalized population, who may have different levels of loneliness, social isolation and health status is needed. Further studies that examine the impact of loneliness and social isolation on healthcare in people with different health conditions are needed, as well as studies that separately analyze visits to the general physician and visits to specialized care. It would be interesting to study if programs for the prevention and management of loneliness and social isolation would reduce healthcare utilization and improve health status. Strengthening the collaboration between social and health services could be helpful since it is possible that lonely people who do not seek help might have an increased risk of having a health problem or mortality, whereas on the other hand lonely people who use the health services frequently may use the services for social reasons. Furthermore, examining pathways linking different social aspects such as loneliness,

social isolation, and social networks with the use of healthcare services, health status, and mortality are necessary. In addition, taking into consideration cultural aspects, gender and age differences are relevant in order to develop a better understanding of the nature of the associations considering the different circumstances of each group. In the specific case of the meta-analysis carried out, it was observed that more research with low risk of bias (i.e. studies that control by health covariates and use validated questionnaires) is required to clarify and fully explore the possible association of loneliness with mortality.

Finally, there is a need for studies that analyze loneliness, social isolation and social networks interventions in view of their effects on different health aspects. A meta-analysis found that interventions focused only on providing social skills did not appear to work; on the contrary, interventions that used particularly cognitive behavioral therapy to correct maladaptive social conditions seemed to reduce loneliness (Masi et al., 2011). Another study concluded that social isolation might be modifiable by creating opportunities for social connections (Coyle and Dugan, 2012). Even though ameliorating loneliness is more complex, it could be possible that reducing social isolation may provide a possibility to develop emotional satisfaction with relationships and therefore reduce feelings of loneliness (Coyle and Dugan, 2012). More studies that focus on interventions for social aspects and also on their effects on health status, healthcare services use, and mortality, are required.

8. CONCLUSIONES

8.1. Conclusiones en español

- La soledad está relacionada con un peor estado de salud, uso frecuente de servicios ambulatorios de salud y mortalidad. El efecto de la soledad sobre los diferentes aspectos de la salud es mayor e independiente del efecto que tienen otras variables relacionadas con las características de la red social y el aislamiento social.
- Un frecuente contacto con los miembros de la red social está relacionado con un mejor estado de salud, mientras que el tamaño de la red y la calidad del contacto con los miembros de la red no lo están.
- La relación entre la soledad y el estado de salud es más fuerte en la población joven que en los adultos mayores. Esta relación no varía por género.
- La soledad, no estar casado y tener contacto menos de una vez al mes con otro miembro de la familia o no tener familia, están asociados al uso frecuente de atención ambulatoria en mujeres. A su vez, ni la soledad ni el aislamiento social están relacionados con un uso frecuente de servicios ambulatorios, en los hombres.
- Ni la soledad ni el aislamiento social están asociados con el ingreso hospitalario en mujeres y en hombres. La frecuencia de contacto con el médico de atención ambulatoria podría fortalecer la relación y ser una fuente de apoyo social para la persona mientras que este hecho no sucedería con los profesionales de cuidados hospitalarios que son visitados menos frecuentemente.
- La soledad está asociada con la mortalidad. Esta asociación es ligeramente más fuerte en hombres que en mujeres. Sin embargo, esta relación desaparece cuando los estudios controlan por el estado de salud o por comorbilidades.

- Un número considerable de estudios que analizaron el efecto de la soledad en la mortalidad no utilizaron cuestionarios validados ni controlaron por variables relacionadas con el estado de salud. Estudios futuros deberán mejorar estos aspectos metodológicos.
- La soledad, el aislamiento social y la red social son características con efectos diferentes que deberían ser analizadas independientemente para su mejor comprensión.
- Se requieren estudios experimentales para testar si existen relaciones causales en las asociaciones encontradas junto con estudios que analicen las vías que vinculan la soledad y las redes sociales a la salud.
- Es necesario investigar el rol mediador de la salud en la relación entre la soledad y la mortalidad, así como si las diferentes condiciones de salud repercuten en el nivel de soledad.
- Futuros estudios cualitativos deberían de ser llevados a cabo para entender la experiencia de la soledad y los posibles factores relacionados con estos sentimientos subjetivos en hombres y en mujeres.

8.2. Conclusiones en inglés

- Loneliness is related to a worse health status, frequent use of outpatient healthcare services, and mortality. The effect of loneliness on those different health related-outcomes is higher and independent from the impact of the social network related variables and social isolation.
- A more frequent contact with the members of the social network is related with a better health status. However, the size of the social network and the quality of the contact within members of the social network are not.
- The relationship between loneliness and health status is stronger in the younger population than in older people. This relationship does not differ by gender.
- Loneliness, being unmarried and having less than monthly contact with other family members or not having other family members, are associated with frequent use of outpatient healthcare services in women. In turn, neither loneliness nor social isolation are related with a frequent outpatient care use for men.
- Neither loneliness nor social isolation are associated to inpatient care use in women and in men. The frequency of contact with the outpatient healthcare physician may strengthen the relationship and might serve as social support to the person while this may not happen with the inpatient care professionals whom are visited less frequently.
- Loneliness is associated with mortality. This association is slightly stronger in men than in women. However, this relationship disappears when the studies controlled for health status or comorbidities.

- A considerable number of studies that analyzed the effect of loneliness on mortality did not use validated questionnaires and did not control for variables related to health status. Future studies should improve these methodological issues.
- Loneliness, social isolation and social network are characteristics with different effects that should be analyzed independently in order to better understand them.
- Experimental studies are needed to show if there are causal relationships in the associations that were found, as well as studies that analyze the pathways from loneliness and social networks to health.
- The mediating role of health conditions in the relationship between loneliness and mortality needs to be further investigated, as well as whether different health conditions have an impact on the level of loneliness.
- Future qualitative studies should be carried out in order to understand the experience of loneliness and factors that are potentially related to these subjective feelings in men and women.

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10. ANNEXES

10.1. Consentimiento informado de los participantes

Consentimiento informado de línea base.

ESTUDIO EUROPEO COURAGE

A. IPSOS Operaciones certifica que:

1. **Las respuestas de su entrevista permanecerán en la más estricta confidencialidad**. Se tratarán anónimamente de acuerdo con la Ley Orgánica del Tratamiento de Datos de carácter personal 15/99 (LORTAD).

2. De acuerdo con la **LEY DE PROTECCIÓN DE DATOS** vigente referida a la protección y tratamiento de datos, **toda la información que nos facilite** en este cuestionario **será tratada exclusivamente con fines estadísticos** no pudiendo ser utilizada de forma nominal ni facilitada a terceros.

3. **Su nombre, dirección y teléfono se guardará separados de sus respuestas a la entrevista. Sólo en forma anónima sus respuestas a la entrevista serán transferidas junto con las de los restantes entrevistados al centro de análisis de datos.**

4. **La entrevista ha sido efectuada por un agente entrevistador de Ipsos Operaciones.**

B. COMO PERSONA ENTREVISTADA PARA ESTE ESTUDIO

1. **Mi participación en la encuesta es voluntaria**.

2. **Se me ha explicado el objetivo del Estudio**.

3. **He respondido libremente, según mi opinión personal, a todas las preguntas que se me han formulado, o bien he dejado de responder cuando así lo he deseado**.

4. **Doy mi conformidad para que en el futuro pueda ser contactado y entrevistado por el Comité Científico del Estudio para contestar otras preguntas acerca de la salud y calidad de vida**.

5. A pesar de lo dicho anteriormente, soy consciente de que no asumo **ninguna obligación** de contestar a ninguna otra cuestión que en el futuro se me quiera plantear sobre este tema.

Fecha : _____ / _____/ _____

Ipsos Operaciones **El Entrevistado**

Entrevista Nº: _____

IPSOS Operaciones, S.A.
Sociedad Unipersonal
Inscrita Registro Mercantil de Madrid Tomo 8385
Gral. 7284 de la secc. 3ª del Libro de Sociedades
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Dr. Josep Maria Haro Abad
Parque Sanitario San Juan de Dios
Sant Boi de Llobregat. Barcelona

Dr. José Luis Ayuso Mateos
Universidad Autónoma de Madrid

Consentimiento informado de la segunda ola.

Estudio sobre envejecimiento saludable

A. El Hospital Universitario de la Princesa, el Parc Sanitari Sant Joan de Déu e Ipsos Operaciones certifican que:

1. Sus respuestas a la entrevista permanecerán en la más estricta confidencialidad. Toda la información recogida se tratará anónimamente de acuerdo con la Ley Orgánica de Tratamiento de Datos de carácter personal 15/99 (LORTAD) [1].
2. De acuerdo con la LEY DE PROTECCIÓN DE DATOS vigente referida a la protección y tratamiento de datos, toda la información que nos facilite en esta entrevista será tratada exclusivamente con fines estadísticos, sin poder ser utilizada de manera nominal ni facilitada a terceros.
3. Su nombre, dirección y teléfono (así como los datos de la persona sobre la que usted nos informe, en su caso) se guardarán de forma separada a las respuestas a la entrevista. Sus respuestas a la entrevista sólo serán transferidas en forma anónima, junto con el resto de entrevistas, al centro de análisis de datos.
4. La entrevista será efectuada por un/a técnico/a de IPSOS Operaciones.

B. Como persona entrevistada en este estudio certifico que:

1. Mi participación en la entrevista es voluntaria.
2. Se me ha explicado el objetivo de este estudio.
3. Mis respuestas son libres, según mi opinión personal, y puedo dejar de responder cuando así lo desee.

Y para que así conste, firmo el presente documento en _____, el _____ de _____ de _____

Nombre y firma del entrevistado/a, testigo o informante proxy

Firma de IPSOS

_____ _____

Número de entrevista: _____

[1] Los participantes en este estudio pueden ejercer en cualquier momento los derechos ARCO para el control sobre sus datos personales (de acceso, rectificación, cancelación, y oposición). Para ello, se puede poner en contacto con Ipsos Operaciones o con el equipo investigador.

Equipo investigador
Teléfono Madrid: 91 497 27 16
Teléfono Barcelona: 93 640 63 50
extensión: 2353

IPSOS Operaciones
Teléfono Madrid: 91 767 21 99
Teléfono Barcelona: 93 452 21 00
Correo electrónico: spain@ipsos.com

10.2. Cuestionario de soledad

3-ITEM UCLA LONELINESS SCALE

Las siguientes preguntas son sobre cómo se siente usted sobre diferentes aspectos de su vida. Para cada una, dígame con qué frecuencia se siente de esa manera.

	RARAMENTE	EN OCASIONES	A MENUDO
Q6351. ¿Con qué frecuencia siente que le falta compañía?	1	2	3
Q6352. ¿Con qué frecuencia se siente solo?	1	2	3
Q6353. ¿Con qué frecuencia se siente aislado de los demás?	1	2	3

10.3. Cuestionario para evaluar las redes sociales

Preguntas para evaluar el tamaño de la red social:

Q6101. Por favor, indique el número de personas (en total) que están tan próximas a usted en el presente que usted: puede hablar con ellas sobre asuntos personales, puede obtener ayuda de ellas en problemas cotidianos, y/o disfruta pasando su tiempo libre con ellas (por favor considere miembros de la familia, amigos, compañeros de trabajo, etc.)	☐ —— —— *-8. No sabe*

Preguntas para evaluar la calidad de las relaciones con los miembros de la red social:

Q6102. ¿Cómo de cercana es su relación con su esposo/a o pareja?	1 Muy cercana 2 Bastante cercana 3 No muy cercana 4 Nada cercana

¿Con cuántas personas de los siguientes grupos usted diría que tiene una relación cercana?			
	Con ninguno	Con algunas personas de este grupo	Con todas las personas de este grupo
Q6111. Padres	1	2	3
Q6112. Hijos	1	2	3
Q6113. Nietos	1	2	3
Q6114. Otros familiares	1	2	3
Q6115. Compañeros de trabajo	1	2	3
Q6116. Amigos	1	2	3
Q6117. Vecinos	1	2	3

Preguntas para evaluar la frecuencia de contacto con los miembros de la red social:

¿Con qué frecuencia en los <u>últimos 12 meses</u> usted ha tenido contactos personales (cara a cara) con…					
	Nunca	Una o alguna vez al año	Una o alguna vez al mes	Una o alguna vez por semana	A diario
Q6211. Esposo/a o pareja?	1	2	3	4	5
Q6212. Padres?	1	2	3	4	5
Q6213. Hijos?	1	2	3	4	5
Q6214. Nietos?	1	2	3	4	5
Q6215. Otros familiares?	1	2	3	4	5
Q6216. Compañeros de trabajo (fuera del lugar de trabajo)?	1	2	3	4	5
Q6217. Amigos?	1	2	3	4	5
Q6218. Vecinos?	1	2	3	4	5
Q6219. Conocidos?	1	2	3	4	5

10.4. Cuestionario para evaluar aislamiento social

Q1012. ¿Cuál es su estado civil actual?	Nunca ha estado casado(a) ……1 Actualmente casado(a) ……...2 Viviendo con su pareja ……3 Separado(a)/divorciado(a) .....4 Viudo(a) 5

¿Con qué frecuencia en los <u>últimos 12 meses</u> usted ha tenido contactos personales (cara a cara) con…	Nunca	Una o alguna vez al año	Una o alguna vez al mes	Una o alguna vez por semana	A diario
Q6213. Hijos?	1	2	3	4	5
Q6212. Padres?	1	2	3	4	5
Q6214. Nietos?	1	2	3	4	5
Q6215. Otros familiares?	1	2	3	4	5
Q6216. Compañeros de trabajo (fuera del lugar de trabajo)?	1	2	3	4	5
Q6217. Amigos?	1	2	3	4	5

¿Con qué frecuencia en los últimos 12 meses usted…	Nunca	Una o dos veces al año	Una o dos veces al mes	Una o dos veces por semana	A diario
Q6613....asistió a una reunión con algún grupo, club u organización?	1	2	3	4	5
Q6618....asistió a actividades religiosas (no incluya bodas y funerales)?	1	2	3	4	5
Q6621 Acudió a centros o asociaciones de mayores (centros de día), grupos de autoayuda, universidades para la tercera edad?	1	2	3	4	5
Q6622 Acudió a clubs deportivos, competiciones deportivas, o hizo deporte con alguien más?	1	2	3	4	5

10.5. Cuestionario para evaluar el uso de servicios de salud

Preguntas para evaluar el uso frecuente de atención ambulatoria.

Q5027. En total, durante los últimos 12 meses, ¿cuántas veces recibió usted alguna atención o consulta médica?	[___l___|___] Veces No sabe …….....-8

Preguntas para evaluar el ingreso hospitalario.

Q5007. ¿Cuántas veces diferentes estuvo usted ingresado(a) en un hospital o un centro de cuidados de larga estancia por lo menos durante una noche en los últimos 12 meses?	[___|___] Veces No sabe …….....-8 “Ninguna noche”..…….……00

10.6. Presentaciones relacionadas con la tesis doctoral en congresos científicos

Congresos Internacionales

XVI World Congress of Psychiatry "Focusing on access, quality and humane care". Madrid, septiembre 2014

L. Rico-Uribe; J.L. Ayuso-Mateos; F.F. Caballero; M. Miret; B. Olaya; J.M. Haro. *Impact of different components of the social network and the subjective perception of loneliness on depression.* Presentación de póster.

Eleventh International Conference of the European Network For Mental Health Service Evaluation (ENMESH), Closing the gap between research and policy in mental health. Málaga, octubre 2015

Rico-Uribe, Laura Alejandra; Caballero, Francisco Félix; Miret, Marta; Martín-María, Natalia; Olaya, Beatriz; Haro, Josep Maria; Ayuso-Mateos, José Luis. *Association of The Subjective Perception of Loneliness and Well-being with Mortality: A Preliminary Analysis.* Presentación de póster.

10.7. Estancias de investigación

Durante los meses de marzo, abril y mayo del 2015 realicé una estancia de investigación en la Organización Mundial de la Salud (OMS). En este periodo estuve participando en el programa de discapacidad y rehabilitación bajo la supervisión de la Profesora Alarcos Cieza. Las actividades que desempeñé fundamentalmente estuvieron relacionadas con la organización de reuniones y la colaboración en la guía de la OMS para la prestación de servicios de rehabilitación y la financiación "*Rehabilitation in health Systems"*.

La segunda estancia la hice en la Universidad Ludwig Maximilians de Múnich, de febrero hasta abril del presente año. En este periodo estuve a cargo de la Doctora Carla Sabariego, y realicé un artículo titulado "La relación de la soledad y el número de contactos sociales con la discapacidad: capacidad y desempeño. Un estudio transversal en Camboya" (The relationship of loneliness and the number of social contacts with disability: capacity and performance. A cross-sectional study in Cambodia). Este artículo será próximamente enviado a una revista indexada.

10.8. Fuentes de financiación para esta tesis

La doctoranda ha recibido una beca de formación en investigación por parte de la Universidad Autónoma de Madrid con el nombre de *"Contratos pre-doctorales para Formación de Personal Investigador, FPI-UAM"* para la realización de la presente tesis doctoral.

Así mismo, este trabajo ha contado con el apoyo del Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), el Séptimo Programa Marco de la Comunidad Europea (FP7/2007-2013) bajo el número 223071 (COURAGE in Europe), el Ministerio de Ciencia e Innovación ACI-Promociona (ACI2009-1010), y el Instituto de Salud Carlos III-FIS (PS09/00295, PS09/01845, PI12/01490 and PI13/00059). Los proyectos PI12/01490 y PI13/00059 fueron cofinanciados por el Fondo Europeo de Desarrollo Regional de la Unión Europea “A Way to Build Europe”.

Las fuentes financiadoras no han tenido ninguna implicación en el diseño del estudio, la recopilación y análisis de datos, la decisión de publicación o la preparación de esta tesis doctoral.

10.9. Publicaciones realizadas durante el doctorado, pero no incluidas en esta tesis

- Domènech-Abella, J., Lara, E., Rubio-Valera, M., Olaya, B., Moneta, M. V., **Rico-Uribe, L. A.,** Ayuso-Mateos J.L., Mundó J. & Haro, J. M. (2017). Loneliness and depression in the elderly: the role of social network. Social psychiatry and psychiatric epidemiology, 1-10.
- Lara, E., Koyanagi, A., Caballero, F., Domènech-Abella, J., Miret, M., Olaya, B., **Rico-Uribe, L. A.,** Ayuso-Mateos J.L. & Haro, J. M. (2017). Cognitive reserve is associated with quality of life: A population-based study. *Experimental gerontology*, *87*, 67-73.
- Martín-María, N., Miret, M., Caballero, F. F., **Rico-Uribe, L. A.**, Steptoe, A., Chatterji, S., & Ayuso-Mateos, J. L. (2017). The Impact of Subjective Well-Being on Mortality: A Meta-Analysis of Longitudinal Studies in the General Population. *Psychosomatic Medicine*.
- Rehabilitation in health systems. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.
- Domènech-Abella J., Perales J., Lara E., Moneta M. V., Izquierdo A., **Rico-Uribe, L. A.**, Mundó J., & Haro J. M. (2017). Socio-demographic factors associated with changes in successful aging in Spain: a follow-up study. Journal of Aging and Health. In press.
- Caballero F. F., Miret M., **Rico-Uribe, L. A.**, Haro J. M. & Ayuso-Mateos J. L. Longitudinal Relationship of Social Networks and Loneliness with Subjective Well-being: A Three-year Follow-up Study. Bajo revisión en la revista Applied Psychology: Health and Well-Being.

- Olaya, B., Domènech-Abella J., Moneta M. V., Lara E., Caballero F. F., **Rico-Uribe, L. A.,** Haro J. M. All-cause Mortality and Multimorbidity in Older Adults: The Role of Social Support and Loneliness. Bajo revisión en la revista The Gerontologist.
- **Rico-Uribe, L. A.**, Ivandic I., Miret M., Caballero F. F., Chhan L., Cieza A., Ayuso-Mateos J. L. & Carla Sabariego. The relationship of loneliness and the number of social contacts with disability: A cross-sectional study in Cambodia. En proceso de envío a la revista Social Science Research.