FACTORS ASSOCIATED WITH LONELINESS:
AN UMBRELLA REVIEW OF OBSERVATIONAL STUDIES

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ABSTRACT

Background: Evidence provides inconsistent findings on risk factors and health outcomes associated with loneliness. The aim of this work was to grade the evidence on risk factors and health outcomes associated with loneliness, using an umbrella review approach.

Methods: For each meta-analytic association, random-effects summary effect size, 95% confidence intervals (CIs), heterogeneity, evidence for small-study effect, excess significance bias and 95% prediction intervals were calculated, and used to grade significant evidence (p<0.05) from convincing to weak. For narrative systematic reviews, findings were reported descriptively.

Results: From 210 studies initially evaluated, 14 publications were included, reporting on 18 outcomes, 795 studies, and 746,706 participants. Highly suggestive evidence (class II) supported the association between loneliness and incident dementia (relative risk, RR=1.26; 95%CI: 1.14-1.40, I^2 23.6%), prevalent paranoia (odds ratio, OR=3.36; 95%CI: 2.51-4.49, I^2 92.8%) and prevalent psychotic symptoms (OR=2.33; 95%CI: 1.68-3.22, I^2 56.5%). Pooled data supported the longitudinal association between loneliness and suicide attempts and depressive symptoms. In narrative systematic reviews, factors cross-sectionally associated with loneliness were age (in a U-shape way), female sex, quality of social contacts, low competence, socio-economic status and medical chronic conditions.

Limitations: low quality of the studies included; mainly cross-sectional evidence.

Conclusions: This work is the first meta-evidence synthesis showing that highly suggestive and significant evidence supports the association between loneliness and adverse mental and physical health outcomes. More cohort studies are needed to disentangle the direction of the association between risk factors for loneliness and its related health outcomes.

Key words: loneliness; meta-analysis; risk factor; health outcome; umbrella review.

1. Background

Loneliness is a perceived deficit between actual and desired quality or quantity of relationships(Cacioppo and Patrick, 2008), which is different from objective social isolation. (Malcolm et al., 2019; Rozzini et al., 2008; Sarason et al., 1986) Several social and clinical factors have been proposed as putative risk factors for loneliness. For instance, these include coping strategies(Perlman and Peplau, 1981), socio-economic status(Wee et al., 2019), psychotic illness(Mushtaq et al., 2014), and depressive disorder(Singh and Misra, 2009), and increased mortality.(Luo and Waite, 2014) In this regard, the association between loneliness and neuro-psychiatric disorders is likely important as literature suggests that anxiety disorders(Anderson and Harvey, 1988), depressive disorders(Green et al., 1992; Prince et al., 1997), schizophrenia spectrum disorders(Sündermann et al., 2014), even in its early phases(Sündermann et al., 2014), Alzheimer's disease(Wilson et al., 2007) and ultimately suicide(Stravynski and Boyer, 2001) have been associated with loneliness, often in a bidirectional way. Also, among subjects with mental illness, loneliness has been associated with more severe symptoms, less recovery and poorer social functioning.(Wang et al., 2018)

However, most studies investigating associations between loneliness and mental or physical health outcomes were cross-sectional, hence precluding any causal inference between loneliness and putative risk factors or health outcomes.(Shioda et al., 2016) For instance, several biases may be affecting studies on aforementioned associations, including publication bias, small sample sizes, excess of significance, or high heterogeneity. Finally, to the best of our knowledge, no umbrella review has graded the available evidence on risk factors and health outcomes of loneliness based on objective criteria, including both meta-analyses and narrative systematic reviews. In this sense, umbrella reviews (i.e. reviews of previously published systematic reviews/meta-analyses consisting in the replication of the meta-analyses following a uniform statistical approach for all factors to allow their comparison) have been created for overcoming the inherent limitations of meta-analyses. (Fusar-Poli and Radua, 2018)

Thus, the aim of the present work is to provide an overview of risk factors and health outcomes nominally associated with loneliness according to systematic reviews and meta-analyses, and - where feasible - to grade the evidence according to strict objective and widely accepted criteria, in the context of an umbrella review.

2. Methods

The protocol for this study was submitted to PROSPERO on 14th November 2019 and enclosed as supplementary material. We performed a systematic review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations (Moher et al., 2009) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.(Stroup et al., 2000)

2.1 Search strategy and selection criteria

We searched PubMed and PsycInfo databases (last search performed on October 16th 2019) to identify systematic reviews or meta-analyses pooling observational (cross-sectional, case-control, cohort) studies examining any association between putative risk factors or mental/physical health outcomes, and loneliness. The following search key was used: "(loneliness) AND (Meta-Analysis[ptyp] OR metaanaly*[tiab] OR metaanaly*[tiab] OR Systematic review [ptyp] OR "systematic review" [tiab])).mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, tc, id, tm, mh]". Two reviewers (DG, NV) independently searched titles/abstracts for eligibility, and assessed the full text of those articles surviving title/abstract phase. A third reviewer resolved any conflict (MS).

When more than one meta-analysis assessed the same risk factor or the same outcome, we only included the one with the larger number of studies, as previously described.(Radua et al., 2018; Raglan et al., 2018; Theodoratou et al., 2014)

Exclusion criteria were: 1) meta-analyses of randomized controlled trials (RCTs); 2) studies published in languages other than English, 3) meta-analyses assessing the association between risk factors or health outcomes and construct similar but different from loneliness, such as social isolation or living alone.

2.2 Data extraction

The same two investigators that performed the screening independently extracted data in a pre-defined excel spreadsheet. For each meta-analysis, we extracted PMID/DOI, first author, publication year, population included in the study, factor associated with loneliness, study design, age of participants, number of included studies and the total sample size.

For each primary study, we recorded information on first author, year of publication, study design (i.e., cohort or case-control), number of cases (subjects suffering from loneliness in studies assessing risk factors, and number of those developing health outcomes in studies assessing loneliness outcomes), adjusted (or unadjusted) effect sizes (ESs), with their 95% confidence intervals (CIs), and study location.

For meta-analyses only providing pooled estimates, we also extracted at meta-analytical level the effect size with 95%CI, and the I^2 as a measure of heterogeneity.

For narrative reviews, we also extracted the narrative synthesis of main results of included studies.

The methodological quality of each included meta-analysis was assessed with the Assessment of multiple systematic reviews (AMSTAR) 2 tool (available at https://amstar.ca/Amstar-2.php), which is a recent update of AMSTAR,(Shea et al., 2017) by same two investigators (DG, NV).

2.3 Data analysis

For each association of meta-analyses providing individual study data, we extracted effect sizes of individual studies and re-performed the meta-analysis calculating the pooled ES and the 95% confidence intervals, with random-effects models to compare homogeneously analyzed results.(DerSimonian and Laird, 1986) Heterogeneity was assessed with the I^2 statistic.(Higgins et al., 2003) Additionally, we calculated the 95% prediction intervals for the summary random ESs providing the possible range in which the ESs of future studies is expected to fall.(Riley et al., 2011)

We also tested the presence of small-study effect bias,(Bortolato et al., 2017; Dragioti et al., 2018; Ioannidis and Trikalinos, 2007; Radua et al., 2018) which is deemed to be present in case of both pooled estimates larger than the individual largest study, and publication bias (Egger's regression asymmetry test (p<0.10)). We finally assessed the existence of excess significance bias by evaluating whether the observed number (O) of studies with nominally statistically significant results ("positive" studies, p<0.05) was different from the expected number (E) of studies with statistically significant results (significance threshold set at p<0.10) (Ioannidis and Trikalinos, 2007; Ioannidis, 2013), a test designed to assess whether the published meta-analyses comprise an over-representation of false positive findings.(Ioannidis and Trikalinos, 2007)

No additional analysis was performed on meta-analyses providing pooled estimates and on narrative systematic reviews.

2.4 Assessment of the credibility of the evidence

Credibility of meta-analyses providing individual study data was assessed according to stringent criteria based on previously published umbrella reviews.(Bortolato et al., 2017; Dragioti et al., 2018; Dragioti et al., 2017; Li et al., 2017; Theodoratou et al., 2014; Veronese et al., 2018) In brief, associations that presented nominally significant random-effects summary ESs (i.e., p < 0.05) were ranked as convincing, highly suggestive, suggestive, and weak evidence based on number of events, strength of the association, and the presence of several biases (criteria available in **Supplementary Table 1**).

Quality of included meta-analyses and narrative systematic reviews were assessed by means of AMSTAR2.

3. Results

3.1 Search

The flow diagram of search, selection and inclusion process is fully reported in **Figure 1**. Out of 269 hits initially identified, after duplicate removal, 206 were assessed at title/abstract level. Fifteen papers were excluded with specific reasons, namely they did not follow a systematic approach of the literature (k=7), they did not focus on loneliness (k=5), or on any health-outcome (k=2) or risk factor, or only included one single study (k=1). Finally, 14 systematic reviews were included in this umbrella review.(Boss et al., 2015; Brown et al., 2018; Chang et al., 2017; Chau et al., 2019; Deckx et al., 2018; Erzen and Cikrikci, 2018; Lara et al., 2019; Michalska da Rocha et al., 2018; Petitte et al., 2015; Pinquart and Sorensen, 2010; Rico-Uribe et al., 2018; Tobin et al., 2014; Valtorta et al., 2016; Wang et al., 2018) The list of references of excluded studies, with reason, is available as **Supplementary Table 2**.

Supplementary Table 3 shows the quality assessment using the AMSTAR 2. Of 14 papers included, one was rated as high quality, nine as moderate, and four as critically low.

3.2 Meta-analyses providing individual studies data

Grading and results of meta-analyses providing individual study data are reported in **Table 1**. Median number of included studies was 13 (range 3 to 31), median sample size was 21,221, three meta-analyses included only cohort studies (Lara et al., 2019; Rico-Uribe et al., 2018; Valtorta et al., 2016), while two meta-analyses included cross-sectional designs.(Chau et al., 2019; Michalska da Rocha et al., 2018) All included meta-analyses reported a significant association of investigated factors with loneliness, but heterogeneity was high in four, small study effect was present in three, prediction intervals included null value in three, and excess of significance bias was present in one. Three associations were supported by highly suggestive evidence (class II), namely prevalent paranoia (i.e. an extreme and unreasonable feeling that other people do not like you or are going to harm or criticize one person, typical of schizophrenia) (k=18, n=33,355, OR 3.36, 95%CI 2.51-4.49, I^2 92.8%) and prevalent psychotic symptoms (i.e. hallucinations, delusions, confused and disturbed thoughts) (k=13, n=2,668, OR 2.33, 95%CI 1.68-3.22, I^2 56.5%), which were based on cross-sectional studies, and incident dementia (k=8, n=3,345, RR 1.26, 95%CI 1.14-1.4, I^2 23.6%), based on cohort studies, over a mean follow-up period of 6.5 years. A significant association also emerged for the association between mortality and incident coronary heart disease, based on cohort studies, but such associations were only supported by suggestive and weak credibility, respectively.

3.3 Meta-analyses providing pooled estimates

Results of the umbrella review of narrative systematic reviews are reported in **Table 2**. Three papers(Chang et al., 2017; Erzen and Cikrikci, 2018; Pinquart and Sorensen, 2010), including seven different outcomes and providing pooled estimates, reported a significant association between loneliness and investigated factors. All meta-analyses included cross-sectional studies. Loneliness was associated with increased suicide attempts, depressive symptoms, with age following a U-shaped curve (i.e. younger and older individuals experienced more frequently loneliness), female gender, poor quality of social network, low competence, and low socio-economic status.

3.4 Narrative systematic reviews

Results of the umbrella review of narrative reviews are reported in **Table 3**. Six narrative systematic reviews(Boss et al., 2015; Brown et al., 2018; Deckx et al., 2018; Petitte et al., 2015; Tobin et al., 2014; Wang et al., 2018) were included in the present umbrella review. Four of them included cross-sectional studies. One included only cohort studies, and one included both cross-sectional and cohort studies. Authors concluded that loneliness was associated with autism, emotion-focused coping strategies, acute stress reactivity, poorer cognitive function in cross-sectional studies, that loneliness increased the risk of depression in longitudinal studies, and with presence of chronic disease according to mixed cross-sectional and cohort studies.

4. Discussion

Our work includes 14 systematic reviews and 18 outcomes, 795 studies, and 746,706 participants. The present umbrella review shows that several risk factors and both mental and physical health outcomes are nominally significantly associated with loneliness. Mental illness, such as autism, and female gender are plausible risk factors for loneliness, while depression, suicide attempts, and dementia are plausible health outcomes associated with loneliness. Mainly cross-sectional evidence focused on the association between loneliness and psychotic symptoms, cognitive functioning, coping strategies, and a number of medical conditions which could either be a risk factor or a consequence of loneliness itself.

We believe that our findings are important for several reasons. First, and most important, loneliness is a highly prevalent condition in adult and older people. It is estimated that the prevalence of loneliness, in North America, may range from 17% to 57% in the general population, being higher in some vulnerable populations such as people suffering from heart disease, depression, anxiety, or dementia.(Lee et al., 2019) Similar data and characteristics have been reported from Europe.(Beutel et al., 2017) Given that this condition is highly prevalent and often associated with negative health outcomes, as also our umbrella review confirms, recently the United Kingdom Government proposed a specific ministry for loneliness.(Pimlott, 2018) At the end of 2017, in fact, an UK government commission helped by more than a dozen non-profit organizations observed that 9 million Britons suffer from loneliness, equal to 14% of the population. (Pimlott, 2018) This "provocative" political action was well-received globally as confirmed by a seminal article in the New York Times defining loneliness as a health epidemy.(Klinenberg, 2018) Second, our umbrella review confirms the important role of loneliness as a potential risk factor for some medical conditions, particularly neurological and psychiatric ones. The re-analysis of already published data shown in our work suggested a highly suggestive evidence (i.e. an evidence poorly biased) supporting the association between loneliness and incident dementia and with prevalent paranoia/psychotic symptoms, and pooled data indicating a significant association between loneliness and suicide attempts and depressive symptoms in longitudinal studies.

Finally, our work also evidenced the importance of some non-medical correlates for loneliness, namely age (in a U-shaped mode), female sex, quality of social contacts, low competence and socio-economic status. Taken together, after excluding non-modifiable factors, our umbrella review supports the importance of social factors in identifying people that can suffer from loneliness, even if this evidence is limited by the cross-sectional nature of these studies. Of particular importance is the association between age and loneliness. Our umbrella review suggests that young (including adolescents and younger people) and old people can have a greater prevalence of loneliness,

compared to middle-aged people. This is probably due to the fact that middle-aged people still work and so the number of social contacts are greater than younger and older people.

As previously observed in a previous overview of systematic reviews without a quantitative assessment of the evidence, some authors proposed some biological explanations that can associate loneliness to the higher presence and incidence of health outcomes.(Leigh-Hunt et al., 2017) Some authors have in fact indicated that loneliness is associated with reduced levels of protective hormones leading to adverse effects on heart rate, blood pressure and the repair of blood vessel walls(Cacioppo and Hawkley, 2003) and to a downregulation of the immune system and to a neuroendocrine dysregulation(Cacioppo and Hawkley, 2003), potentially justifying the epidemiological evidence that we found in our work. Moreover, people experiencing loneliness may be more likely to initiate harmful health behaviors such as smoking, excess alcohol consumption, overeating or food restriction as a psychological relief mechanism and all of them are well-known risk factors and correlates for psychiatric conditions.(Alderete et al., 2000; Bolzetta et al., 2019) Moreover, loneliness has been shown to be associated with poor physical activity,(Schrempft et al., 2019) which in turn is cross-sectionally and longitudinally associated with depression and psychosis among other mental health outcomes.(Stubbs et al., 2016; Stubbs et al., 2018; Veronese et al., 2017) Hence low physical activity might have mediated or moderated the association between loneliness and health outcomes. Loneliness has been shown to be associated with psychosis throughout the whole course of psychosis, since the very beginning of psychotic symptoms, namely from at risk mental state(Robustelli et al., 2017) to multi-episode schizophrenia.(Mote et al., 2019) Subjects with psychosis predominantly show negative symptoms in the long term, which are responsible for the poor functioning together with impaired cognitive function.(Bucci et al., 2018; Giordano et al., 2018; Strauss et al., 2019) Hence, given the relevance of poor social interactions with a potential involvement of loneliness in maintaining negative symptoms, a pilot study has also started to target loneliness in subjects at risk for psychosis, confirming that loneliness is a clinically relevant construct not only in the elderly population, but also in young subjects at risk or with early phases of mental illness.(Lim et al., 2019) However, these hypotheses, mainly based on observational data, must be confirmed by large collaborative long-term cohort studies adjusting for confounders,(Leigh-Hunt et al., 2017) and any role of loneliness in the treatment of negative symptoms of young subjects at risk for psychosis, or with psychosis should be tested in well-designed and adequately powered randomized controlled trials.

Finally, our work introduce which types of healthcare, public health or societal-level interventions can be used effectively to combat loneliness. In this regard, literature suggests a very limited number of interventions able to reverse/fight against loneliness. Moreover, as shown in an interesting narrative review, several interventions reporting some success in reducing social isolation

and loneliness were characterized by a low quality of evidence.(Gardiner et al., 2018) Factors that seem to be significnatly associated with the most effective interventions in reducing loneliness included adaptability, a community development approach, and productive engagement, particularly in older people. (Gardiner et al., 2018) However, more studies are needed, involving larger populations, in order to confirm the efficacy of these public health interventions in improving a so frequent condition.

4.1 Limitations

The strength of the present work is it being the first umbrella review providing a qualitative evidence synthesis on the risk factors and health outcomes associated with loneliness, including both meta-analyses and narrative systematic reviews. Second, it applies stringent quantitative criteria to grade the evidence. Third, it indicates future research directions in order to accumulate evidence to eventually reach convincing evidence threshold for risk factors or health outcomes related with loneliness. The main limitations of the present work are related to the included studies. Specifically, two out of three among the associations reached highly suggestive evidence, as well as evidence from narrative systematic reviews yield from cross-sectional studies. Hence, any direction cannot be inferred from such study designs, and both prevalent paranoia and psychotic symptoms could either be risk factors or health outcomes associated with loneliness.

4.2 Conclusion and future directions

In conclusion, there is highly suggestive evidence from meta-analyses that loneliness increases the risk of dementia, and that paranoia and other psychotic symptoms could either be a risk factors or a health outcome associated with loneliness. Moreover, meta-analyses providing only pooled data show that loneliness is associated with depressive symptoms and suicide attempts. Narrative systematic reviews suggest that loneliness increases the risk of depression, and that cognitive function, coping strategies, and medical conditions are associated with loneliness. More longitudinal cohort studies matching subjects for a multi-dimensional propensity score should assess risk factors and health outcomes associated with loneliness.

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Figure legend

Figure 1. PRISMA flow-chart