Loneliness, social network size and mortality in older adults: a meta-analysis

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Abstract
Loneliness and social network size have been found to be predictors of mortality in older adults. The objective of this study was to investigate whether loneliness and small social network size are associated with an increased mortality risk and to review the evidence for either network size, or loneliness that constitutes the higher mortality risk. A systematic literature search was performed in PubMed, EMBASE and PsychInfo in January/February 2018 and March/April 2021. Studies that mentioned outcome data were included in the meta-analysis and coded using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies. The meta-analysis showed that both loneliness and small social network size are associated with mortality risk in older adults (Hazard Ratio 1.10 (95% Confidence Interval 1.06–1.14) for loneliness and 0.96 (95% Confidence Interval 0.93–0.99) for larger network size). Sensitivity analyses according to the Newcastle–Ottawa Quality Assessment Scale yielded varying results. Heterogeneity was large. In conclusion, both loneliness and small social network size in older adults are associated with increased mortality, although the effect size is small. Targeting subjective and objective aspects of older adults’ social contacts should be on the agenda of preventive as well as personalized medicine. In order to be able to compare the association between loneliness and network size and mortality, more studies are needed that include both these risk factors.

Keywords Loneliness · Social isolation · Social network · Mortality

Introduction
It has long been recognized that social relationships have an impact on health and mortality (House et al. 1988; Olsen et al. 1991; Penninx et al. 1997). Both subjective and objective aspects of social relationships are important in this respect. The subjective feeling of missing an intimate relationship or missing a wider social network is recognized as loneliness (Jong and Tilburg 2006). On the other hand, objective indicators of social relationships reflect a small social network size (O’Luanaigh and Lawlor 2008; Routasalo et al. 2004; Shankar et al. 2011; Steptoe et al. 2013), the absence of a spouse, low frequency of social contacts and lack of participation in social groups (Cacioppo

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et al. 2015). These objective indicators can be grouped under the term social isolation. Loneliness and social isolation are related, although the association has been found to be rather weak (Cornwell and Waite 2009).

Both subjective and objective aspects of social relationships have been argued to be important predictors of increased mortality in older adults, although results have been inconsistent. Whereas associations between loneliness and mortality have been found in some studies (Holwerda et al. 2012; Luo et al. 2012; Patterson and Veenstra 2010; Penninx et al. 1997; Perissinotto et al. 2012; Shiovitz-Ezra and Ayalon 2010), other studies concluded that mortality was not increased in lonely older adults (Holwerda et al. 2016; Steptoe et al. 2013). Associations between social isolation and mortality have also been found (House et al. 1988; Steptoe et al. 2013; Tanskanen and Anttila 2016), with the effect size of the lack of social relationships on mortality being comparable to that of smoking, obesity and lack of exercise. However, one study concluded there was no significant association between social isolation and mortality (Cerhan and Wallace 1997).

The mechanisms underlying an association between both loneliness and social isolation and mortality are not clear. Possible explanations generally include two mechanisms: through the stress-buffering effects of social connections, or the direct biological effects of the stress of loneliness or lack of contacts (Holt-Lunstad et al. 2010; House et al. 1988). Potential biological mechanisms that have been studied include cognitive decline (Holwerda et al. 2014; Lara et al. 2019; Rafnsson et al. 2020), immune dysregulation (Jaremka et al. 2013, 2018; O’Luanaigh and Lawlor 2008), sleep disturbances (Cacioppo et al. 2002; O’Luanaigh and Lawlor 2008), increased food intake (Jaremka et al. 2018), endocrine dysregulation (Adam et al. 2006; Steptoe et al. 2004) and cardiovascular disease (Cacioppo et al. 2002; Hawkley et al. 2006, 2010; O’Luanaigh and Lawlor 2008; Steptoe et al. 2004). Examples of the stress-buffering effects of social connections are the promoting of adaptive behavior and the availability of instrumental support in case of stress (Holt-Lunstad et al. 2010; House et al. 1988).

To evaluate the associations between both loneliness and social isolation and mortality, systematic reviews and meta-analyses have been done (Holt-Lunstad et al. 2010, 2015; Rico-Uribé et al. 2018). These studies showed that both objective and subjective aspects of social relationships influence mortality in adults. However, many studies that were included in these meta-analyses used a ‘social network index’ (Berkman and Syme 1979), considering not only the number of social ties but also their relative importance. This index has been used by several authors (Kawachi et al. 1996; Schoenbach et al. 1986; Seeman et al. 1987). The problem with using an index is that it obscures which aspects are responsible for the outcome (Avlund et al. 1998). In contrast, our goal was to investigate whether studies that have focused on the association between social relations and mortality provide more evidence in this association for objective aspects or for subjective aspects of social relationships. This division into objective and subjective aspects is in agreement with most research into the effects on health and mortality of loneliness and social relationships, as most researchers focus either on the more objective quantitative measure of network size and diversity, reflecting reduced social network size and paucity of social contact (Shankar et al. 2011; Steptoe et al. 2013), or on the subjective psychological experience of loneliness (Hawkley & Cacioppo 2010; Routasalo et al. 2004; Shankar et al. 2011; Steptoe et al. 2004, 2013). In addition, many studies included in previous meta-analyses did not adjust for covariates. Moreover, because of the inconsistent outcomes of studies into the associations between mortality and both loneliness and social isolation in older adults, we were especially interested in a meta-analysis including studies in older adults only.

The distinction between objective and subjective aspects of social relationships and their associations with mortality in older adults are the main focus of the present study. The number of people in a person’s network can be seen as an indication of social isolation (Victor et al. 2000) and although some research revealed a stable total network size over a four-year period (Van Tilburg 1998), over longer periods of time this network size has been reported to decrease with age (Bowling et al. 1991; Broese van Groenou et al. 2013). Although living alone has been used as an operationalization of social isolation (Victor et al. 2000) and is one of the aspects of social isolation that is associated with increased mortality (Holt-Lunstad et al. 2015), we were especially interested in the question whether there is more evidence for objective aspects or for subjective aspects of social contacts in the association with mortality. Loneliness is often regarded as the subjective counterpart to the objective social isolation (Steptoe et al. 2013; Victor et al. 2000) and it has been reported to increase with age (Victor et al. 2000; Dykstra et al. 2005). Loneliness and depression are related but separate concepts that have strong reciprocal influences in middle-aged and older adults (Cacioppo et al. 2006; Holvast et al. 2015; Peerenboom et al. 2015), and depression has been found to be associated with increased mortality (Li et al. 2019; Wei et al. 2019). Therefore, the presence of depression is an important covariate in the association between loneliness and mortality.

Our main research questions are: 1. Are subjective (loneliness) and objective aspects (small social network size) associated with increased mortality in older adults? 2. Is there more evidence for subjective or for objective aspects of social relations in this association? 3. Do these associations remain when controlled for important covariates such as depression?
Method

Search strategy and selection criteria

To identify studies investigating the mortality effects of loneliness and/or social network size, we systematically searched PubMed in January/February 2018 and in March/April 2021 using the following search: ("Mortality"[Mesh:noexp] OR "mortality"[Subheading] OR mortality*[tiab]) AND ("Aged"[Mesh] OR elderly*[tiab] OR old people*[tiab] OR older adult*[tiab] OR late-life*[tiab] OR late-life*[tiab] OR very old*[tiab] OR old patient*[tiab] OR old person*[tiab] OR aging*[tiab] OR ageing*[tiab] OR octogenarian*[tiab] OR octogenarian*[tiab] OR centenarian*[tiab] OR geriatric*[tiab] OR older patient*[tiab] OR old age*[tiab]) AND ("Loneliness"[Mesh] OR "Social Isolation"[Mesh] OR "Social Support"[Mesh] OR lonely*[tiab] OR lonelines*[tiab] OR social isolation*[tiab] OR social contact*[tiab] OR social network*[tiab] OR social support*[tiab] OR psychosocial support system*[tiab]) AND EMBASE and PsychInfo using the following search terms: aged, elderly, older people, older adult, older patient, late-life, very old, old patient, old person, old age, aging, ageing, octogenarian, octogenarian, centenarian, geriatric, geriatrics, geriatric patients, elder care; combined with loneliness, lonely, social isolation, social networks, social support, social contact, psychosocial support system, social interaction, social behavior, psychosocial factors, social participation, community network, care network, community health network; combined with mortality, death and dying.

When conceptualizing social isolation, several aspects deserve consideration. An important issue is what constitutes the ‘active ingredient’ (Cornwell and Waite 2009) of the lack of social relationships responsible for the association with morbidity and mortality. Different measures of a lack of social relationships have been proposed by different researchers, including living alone, having a small social network, low participation in social activities, low frequency of contacts, perceived lack of social support and feelings of loneliness (Cornwell and Waite 2009), and different aspects of social relationships can be taken into account, such as the existence and quantity of relationships, their formal structure and the actual content (House et al. 1988). To be clear about the ‘active ingredient’ and to oppose objective and subjective aspects of social relationships, we chose network size as the most readily measurable objective indicator of social isolation.

There was no preregistered protocol.

Study selection

Figure 1 shows the flow diagram. Studies were included when they were original studies; in English, French, German or Dutch; had been published in peer reviewed journals; answered the following research question: ‘in older adults, is there an association between loneliness and/or social network size and mortality?’ The exclusion criteria were: age younger than 60 years at start of the study; case reports; systematic reviews and meta-analyses; no measure for loneliness or social network size; lack of information about covariates. In a first selection round, studies were identified with title/abstract using the above-mentioned criteria. This selection was done by two authors (NS and HC or NS and JD). When their opinion differed, a third author was consulted (TH). In the second round, abstracts were examined and if they were not informative enough about the study design, the method section of the full text was read. This was done by two authors (NS and TH or NS and JD). When their opinion differed, a third author (MS) was consulted. Differences in opinion mainly regarded the use of a social network size measure.

Data extraction

In the third round, articles were coded using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies (Wells et al. 2000) (NOS) (Table 1) to evaluate the quality of the studies by assessing potential bias. Each article was coded by the first author (NS) and another author (TH, MS or JD). When there was difference in opinion, a third author (HC) was consulted.

When outcome data were mentioned we included the study in the meta-analysis. Data extraction was done by two authors (NS and TH). In case of studies including also younger adults, we contacted the authors and asked for data concerning only older adults. We extracted adjusted Hazard Ratios from all included studies. When no Hazard Ratio or Relative Risk was mentioned, we estimated the Hazard Ratio using p value, total events and numbers of participants in both groups of participants (Tierney et al. 2007) and calculated the 95% Confidence Interval using the standard error. From every study, the following data were recorded: country, study population, number of participants, age group studied, length of follow-up, Hazard Ratio/Odds Ratio, 95% Confidence Interval and covariates (Table 2).

Statistical analysis

All studies mentioning Hazard Ratio or Relative Risk and a Confidence Interval, or offering enough data to estimate a Hazard Ratio, were included in the meta-analysis (Table 2). Separate analyses were done for loneliness and network size, using the random effects model. Additionally, we executed sensitivity analyses. Firstly, we examined the effect of depression on the association between mortality and loneliness/social network size by first including only studies with depression.
as a covariate, followed by including only studies without depression as a covariate. The same method was used for examining the effect of a social network variable in the association between mortality and loneliness. Similarly, we examined whether differences in scores on items from the NOS influenced the meta-analysis outcome. This was assessed by grouping the studies according to NOS-scores. Additionally, heterogeneity was assessed using Cochran’s Q test at significance level of $p < 0.05$ and quantified by the $I^2$ statistic, with the following rough interpretation: a value of less than 40% indicating little heterogeneity, 30–60% indicating moderate heterogeneity, 50–90% substantial heterogeneity and 75–100% considerable heterogeneity (Deeks et al. 2008). The interpretation of the $I^2$ statistic depends on several factors, such as the significance level and the magnitude of effects (Deeks et al. 2008). Additional sensitivity analyses were executed to examine possible causes of heterogeneity. Publication bias was assessed in funnel plots. We executed the meta-analysis using Comprehensive Meta-Analysis (CMA) software.

**Results**

Of 144 publications that initially fitted our inclusion criteria, 110 did not fit on closer examination (Fig. 1). The most frequent reason for non-inclusion was a different measure for social isolation. For example, authors used measures like frequency of contact, relationship quality, a ‘social index’ or ‘social integration index,’ living situation, social support measure, network type and marriage status. Another frequent reason for exclusion was that the age of included participants was younger than 60 years old and the authors could not provide additional analyses for participants aged 60 and over. Eight studies had to be excluded because they did not include quantitative results. Two studies were retrieved from citation searching, leading to a total of 36 studies.

**Meta-analysis**

Table 2 shows studies included in the meta-analysis. There was some overlap in studies: three publications were based on data from the Longitudinal Aging Study Amsterdam, two publications on data from the Collaborative Research on Ageing in Europe, two publications on data from the Jerusalem Longitudinal Cohort Study and two publications on data from the Kaiser Permanente Northwest study, although data were from different waves and/or different endpoints in time. Using the NOS, all included studies but five appeared to be of good quality; only the study by Drageset et al. (2012) was of fair quality due to the fact that the study investigated nursing home patients only.
and consequently the participants had a higher mortality risk, whereas the studies by Aguiar et al. (2020), Ng et al. (2021), O’Suilleabhain et al. (2019) and Youm et al. (2021) were of poor quality, due to missing information about assessment of outcome and about participants lost to follow-up (Table 3).

### Table 1  
Newcastle–Ottawa Quality assessment scale criteria including attribution of points

| Criteria:                          | Points to be gained |
|-----------------------------------|---------------------|
| **Selection**                     |                     |
| Representativeness                |                     |
| Truly                             | 1                   |
| Somewhat                          | 1                   |
| Selected group                    | 0                   |
| No description                    | 0                   |
| Selection of non-exposed cohort   |                     |
| Drawn from same community         | 1                   |
| Drawn from a different source     | 0                   |
| No description                    | 0                   |
| Ascertainment of exposure         |                     |
| Secure record                     | 1                   |
| Structured interview              | 1                   |
| Written self-report               | 0                   |
| No description                    | 0                   |
| Demonstration that outcome not present at start | 1 |
| Yes                               | 1                   |
| No                                | 0                   |
| **Comparability**                 |                     |
| Comparability of cohorts          |                     |
| Study controls for most important factor | 1 |
| Study controls for additional factors | 1 |
| **Outcome**                       |                     |
| Assessment of outcome             | 1                   |
| Independent blind assessment      | 1                   |
| Record linkage                    | 1                   |
| Self-report                       | 0                   |
| No description                    | 0                   |
| Follow-up long enough?            |                     |
| Yes                               | 1                   |
| No                                | 0                   |
| Adequacy of follow-up             |                     |
| 0                                 |                     |
| Complete follow-up                | 1                   |
| Small number lost/description provided | 1 |
| Higher number lost/no description | 0                   |
| No statement                      | 0                   |

### Loneliness and mortality

We included 28 studies investigating the association between loneliness and mortality. Three studies did not calculate Hazard Ratios but other effect sizes. Since they mentioned $p$ value, total events and numbers of participants in both groups of participants, we were able to estimate a Hazard Ratio using the method described by Tierney et al. (2007) (See Supplement for the formulas used). In 18 studies (Table 2), loneliness was not associated with mortality after controlling for a number of covariates. All studies controlled for age and gender. All studies controlled for (self-assessed) physical health, (chronic) diseases, comorbidity and/or medical conditions. Of the 28 studies, 13 controlled for depression and/or depressive symptoms and 16 studies controlled for a ‘social contact’ variable. Figure 2A shows the forest plot: overall, it shows a small but significant positive association between loneliness and mortality. That the overall analysis shows a positive association could be due to the positive studies showing more robust results, as displayed in Fig. 2A.

### Network size and mortality

We included ten studies investigating the association between network size and mortality (Table 2). All but two showed a lower mortality when the network was larger. All studies controlled for age and gender and (self-rated) physical health, comorbidity or chronic diseases. Seven studies controlled for depression diagnosis or depressive symptoms. None of the studies controlled for loneliness. Figure 2B shows the forest plot: overall, it shows a small but significant negative association between network size and mortality, with a larger network showing a lower mortality risk.

### Sensitivity analyses

Table 4 shows the results of the sensitivity analyses according to covariates and according to NOS-scores. The second and sixth columns show the number of loneliness and network size studies. When only studies that included depression as a covariate were grouped into the meta-analysis, the association with mortality did not change for loneliness: HR was 1.13, 95% CI 1.06–1.22 (original HR 1.10) and decreased for network size: HR was 0.88, 95% CI 0.80–0.97 (original HR 0.96). Introduction of a ‘social contact variable’ diminished the association between loneliness and mortality (HR 1.04).
Table 2  Studies included in the meta-analysis

| Study                | Country     | Study name                                   | Study population                              | Nr. of participants | Age          | Assessment of loneliness/network size | Length of follow-up | OR/HR/RH/RR | Result | Main covariates                                                                 |
|---------------------|-------------|----------------------------------------------|-----------------------------------------------|---------------------|--------------|----------------------------------------|---------------------|-------------|--------|--------------------------------------------------------------------------------|
| Aguiar et al. (2020) | USA         | Kuakini Honolulu Heart Program               | Japanese-American men in Honolulu            | 3186                | 71–93        | Single question                        | 28 yrs              | HR          | 1.29   | Age, cardiovascular risk factors, chronic diseases                            |
| Conde-Sala et al. (2020) | Europe     | Survey of Health, Ageing and Retirement in Europe | 14 European countries                        | 35,604              | ≥60          | 3-item UCLA loneliness scale           | 2 yrs               | HR          | 1.27   | Age, gender, marital status, depressive symptoms, self-rated health, presence of diseases |
| Drageset et al. (2012) | Norway     | –                                            | Nursing home residents                       | 227                 | ≥65          | Social Provisions Scale                | 5 yrs               | HR          | 0.96 (attachment)                | Gender, age, marital status, comorbidity, social integration, GDS-score |
| Ellwardt et al. (2015) | Netherlands | Longitudinal Aging Study Amsterdam           | Nationally representative                    | 2462                | ≥60          | De Jong Gierveld loneliness scale      | ≤20 yrs             | HR          | NS     | Age, mental health, physical health                                          |
| Elovainio et al. (2017) | UK         | UK Biobank Study                             | Within sensible distance from assessment center | 178,769             | ˃60          | 2 questions                            | 8 yrs               | HR          | 1.44   | Age, gender, chronic disease                                                  |
| Holwerda et al. (2012) | Netherlands | Longitudinal Aging Study Amsterdam           | Nationally representative                    | 2433                | ≥60          | De Jong Gierveld loneliness scale      | 19 yrs              | HR          | NS     | Age, gender, marital status, network size, depression, chronic diseases      |
| Holwerda et al. (2016) | Netherlands | Amsterdam Study of the Elderly               | Urban                                         | 4004                | ≥60          | Single question                        | 10 yrs              | HR          | 1.30 (men) 1.04 (women) | Age, social isolation, CVA, diabetes, depression, other diseases |
|                      |             |                                              |                                               |                     |              |                                        |                     |             |        |                                                                                |
| Study                  | Country     | Study name                          | Study population                      | Nr. of participants | Age       | Assessment of loneliness/network size | Length of follow-up | OR/HR/RR/ RH/RR | Result | Main covariates                                                                 |
|-----------------------|-------------|-------------------------------------|---------------------------------------|---------------------|-----------|----------------------------------------|---------------------|---------------|--------|--------------------------------------------------------------------------------|
| Hoogendijk et al. (2020) | Netherlands | Longitudinal Aging Study Amsterdam | Nationally representative             | 1427                | ≥65       | De Jong Gierveld loneliness scale      | 22 yrs              | HR            | NS      | Age, partner status, sex, depression score, social participation, chronic diseases |
| Iecovich et al. (2011)  | Israel      | Jerusalem Longitudinal Study        | Nationally representative             | 605                 | 70–88     | Single question                        | 18 yrs              | HR            | NS      | Gender, health, network type, morbidity, self-rated health (age cohort)          |
| Julsing et al. (2016)  | Netherlands | Zutphen Elderly Study               | Small town men                        | 719                 | 64–84     | De Jong Gierveld loneliness scale      | 25 yrs              | HR            | NS (moderate) | Age, chronic disease                                                            |
| Jylha and Aro (1989)   | Finland     | –                                   | Urban                                 | 1060                | 60–89     | Single question                        | 6.5 yrs             | RH            | NS      | Age, gender, baseline health status, social participation                       |
| Lara et al. (2020)     | Spain       | Collaborative Research on Ageing in Europe | Nationally representative             | 4467                | ≥60       | 3-item UCLA loneliness scale          | 6–7 yrs             | HR            | NS      | Sex, age, depression, social activities                                          |
| Luo and Waite (2014)   | China       | Chinese Longitudinal Healthy Longevity Survey | Nationally representative             | 14,072              | ≥65       | Single question                        | 6 yrs               | HR            | 1.04   | Age, gender, self-assessed health, living arrangement social activities         |
| Ng et al. (2021)       | Singapore   | Panel on Health and Ageing of Singaporean Elderly | Nationally representative             | 4536                | ≥60       | 3-item UCLA loneliness scale          | 6 yrs               | HR            | 1.40 (women) NS (men) | Age, gender, total number of morbidities, social network size, social engagement, living arrangements |
| Study           | Country        | Study name                                      | Study population               | Nr. of participants | Age    | Assessment of loneliness/network size | Length of follow-up | OR/HR/RH/RR | Result | Main covariates                                                                 |
|-----------------|----------------|------------------------------------------------|--------------------------------|---------------------|--------|---------------------------------------|---------------------|-------------|--------|--------------------------------------------------------------------------------|
| Novak et al. (2020) | Sweden         | Gothenburg H70 Birth Cohort Studies Collaborative | Urban                          | 512                 | 70     | Single question                       | 12 yrs              | HR          | NS     | Health, health-related behavioral factors, living alone, physical disease, depression |
| Olaya et al. (2017) | Spain          | Research on Ageing in Europe                    | Nationally representative      | 2113                | ≥ 60   | 3-item UCLA loneliness scale         | 3 yrs               | HR          | NS     | Age, gender, marital status, depression, social support, physical conditions     |
| Olsen et al. (1991)  | Denmark        | –                                               | Urban, experimental group      | 1752                | 70–100 | Single question                       | ≤ 15 yrs            | HR          | NS     | Age, gender, health indicators, social contacts                                   |
| O’Suilleabhain et al. (2019) | Germany       | Berlin Aging Study                              | Urban                          | 413                 | 70–103 | UCLA 8 items                          | 16–19 yrs           | HR          | NS     | Age, sex, marital status, depressive illness                                      |
| Perissinotto et al. (2012) | USA           | –                                               | Nationally representative      | 1604                | ≥ 60   | 3-item UCLA loneliness scale         | 6 yrs               | HR          | 1.45   | Age, gender, marital status, living arrangement, depression, medical conditions |
| Schutter et al. (2020) | Netherlands   | Netherlands Study on Depression in Older adults  | Depressed and control group    | 443                 | ≥ 60   | De Jong Gierveld loneliness scale    | 6 yrs               | HR          | NS     | Age, sex, partner status, depression, chronic diseases                           |
| Steptoe et al. (2013) | England        | English Longitudinal Study of Ageing            | Nationally representative      | 6500                | ≥ 60   | 3-item UCLA loneliness scale         | 7–8 yrs             | HR          | NS     | Age, gender, marital status, general health, depression, CES-D rating, longstanding illness, social isolation |
| Study                          | Country | Study name                                      | Study population | Nr. of participants | Age    | Assessment of loneliness/network size | Length of follow-up | OR/HR/RH/RR | Result | Main covariates                                                                 |
|-------------------------------|---------|------------------------------------------------|------------------|---------------------|--------|----------------------------------------|---------------------|-------------|--------|--------------------------------------------------------------------------------|
| Stessman et al. (2014)        | Israel  | Jerusalem Longitudinal Cohort Study            | Urban            | 1566                | 70–90  | Single question                        | 7 yrs               | HR          | NS     | Gender, marital status, self-rated health, age group, Depression               |
| Sugisawa et al. (1994)        | Japan   | –                                              | Nationally representative | 2200                | ≥ 60   | Single question                        | 3 yrs               | HR          | NS     | Gender, age, marital status, self-rated health, chronic diseases, social contacts, social participation |
| Tabue Teguo et al. (2016)     | France  | Personnes Âgées Quid                            | Nationally representative | 3620                | ≥ 65   | Single question                        | ≤ 22 yrs             | OR          | NS     | Age, gender, living alone, chronic diseases                                   |
| Tanskanen et al. (2016)       | Finland | Living Conditions Survey of 1994                | Nationally representative | 1731                | ≥ 60   | Single question                        | ≤ 17 yrs             | HR          | NS     | Age, gender, self-reported health, social isolation                           |
| Tilvis et al. (2011)          | Finland | –                                              | Nationally representative | 3687                | ≥ 75   | Single question                        | < 5 yrs              | HR          | 1.17   | Age, gender, subjective health                                                |
| Wang et al. (2020)            | England | Cambridge City over-75 s Cohort                | Urban            | 665                 | ≥ 75   | Single question                        | 10 yrs              | HR          | NS     | Age, sex, marital status, chronic diseases, depression                        |
| Youm et al. (2021)            | South Korea | Korean Social Life, Health and Aging Project | Rural            | 679                 | ≥ 60   | Single question                        | 8 yrs               | HR          | 1.31   | Sex, living with spouse, comorbidity, physical health, depression            |
| Network size                  | USA     | Chicago Health and Aging Project               | Urban            | 6497                | ≥ 65   | Single question                        | 10 yrs              | HR          | 1.01   | Age, gender, marital status, medical conditions                              |
| Study                        | Country            | Study name                                       | Study population     | Nr. of participants | Age          | Assessment of loneliness/network size | Length of follow-up | OR/HR / RH/ RR | Result     | Main covariates                                                                 |
|------------------------------|--------------------|-------------------------------------------------|----------------------|---------------------|--------------|---------------------------------------|---------------------|----------------|------------|--------------------------------------------------------------------------------|
| Cerhan and Wallace (1997)    | USA                | Iowa 65 + Rural Health Study                    | Rural               | 2575                | 65–102       | Single question                       | 8 yrs               | HR             | NS (men) NS (women)                                      | Age, major illness, depressive symptoms, self-perceived health |
| De Brito et al. (2017)       | Brazil             | Health, Well-being and Aging Study              | Nationally representative | 1413                | ≥ 60         | Single question                       | 4 yrs               | HR             | 0.67       | Age, gender, living arrangements, comorbidity, depressive symptoms              |
| Ellwardt et al. (2015)       | Netherlands        | Longitudinal Aging Study Amsterdam              | Nationally representative | 2462                | ≥ 60         | Single question                       | ≤ 20 yrs           | HR             | 0.99       | Age, mental health, physical health                                           |
| Giles et al. (2005)          | Australia          | Australian Longitudinal Study of Aging          | Nationally representative | 1477                | ≥ 70         | Combined networks (4)                 | 10 yrs             | HR             | 0.95       | Age, gender, comorbidity conditions, self-rated health, CES-D score            |
| McLaughlin et al. (2011)     | Australia          | Men, Women and Aging Project                    | Urban               | 6877                | 69–87        | Duke Social Support Index              | 5–10 yrs           | RR             | 0.89       | Age, marital status, chronic disease                                         |
| Roth (2020)                  | USA                | National Social Life, Health and Aging Project  | Nationally representative | 2553                | ≥ 60         | Single question (core discussion network name generator) | 5–6 yrs           | HR             | 0.90       | Sex, age, marital status, depressive symptoms                                |
| Schutter et al. (2020)       | Netherlands        | Netherlands Study of Depression in Older Adults  | Depressed and control group | 443                 | ≥ 60         | Close Persons Questionnaire            | 6 yrs               | HR             | NS         | Age, sex, partner status, depression, chronic                               |
| Shye et al. (1995)           | England            | Kaiser Permanente Northwest Region              | Members of Health Maintenance Organization group | 455                 | ≥ 65         | Single question                       | 15 yrs              | RH             | 1.65 (men) 1.61 (women) (small network) | Age, gender, marital status, health                                |
| Vogt et al. (1992)           | USA                | Northwest Kaiser Permanente                     | Members of HMO group | 451                 | ≥ 60         | 4 questions                           | 15 yrs              | RH             | 2.0 (small network)                                      | Age, gender, baseline subjective health                          |

*OR* odds ratio, *HR* hazard ratio, *RH* relative hazard, *RR* relative risk
| Study Loneliness | Representativeness | Selection | Comparability | Outcome | Total |
|------------------|-------------------|-----------|--------------|---------|-------|
|                  |                   | Non-exposed cohort | Ascertainment of exposure | Outcome of interest not present at start | On the basis of design or analysis | Assessment of outcome | Follow-up long enough | Adequacy of follow-up |
| Aguiar et al. (2020)  | 1  | 1 | 1 | 1 | 2 | 0 | 1 | 0 | 7 |
| Conde-Sala et al. (2020) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Drageset et al. (2012) | 0  | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 7 |
| Ellwardt et al. 2015 | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Elowainio et al. (2017) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Holwerda et al. (2016) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Holwerda et al. (2012) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Hoogendijk et al. (2020) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Iecovich et al. (2011) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Julsing et al. (2016) | 0  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Jylha and Aro (1989)  | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Lara et al. (2020) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Luo and Waite (2014) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Ng et al. (2021) | 1  | 1 | 1 | 1 | 2 | 0 | 1 | 0 | 7 |
| Novak et al. (2020) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Okaya et al. (2017) | 0  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Oden et al. (1991) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| O’Suilleabhain et al. (2019) | 1  | 1 | 1 | 1 | 2 | 0 | 1 | 0 | 7 |
| Perissinotto et al. (2012) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Schuit et al. (2020) | 1  | 1 | 1 | 1 | 2 | 0 | 1 | 0 | 8 |
| Steptoe et al. (2013) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Stessman et al. (2014) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Sugisawa et al. (1994) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 |
| Tabue Teguo et al. (2016) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 9 |
| Tanskanen et al. (2016) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
| Tilvis et al. (2011) | 1  | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 |
The first NOS-criterion is ‘representativeness of the exposed cohort.’ This refers to the degree in which the participants are representative of all older adults in the community. With regard to representativeness, the grouping of studies had different effects for loneliness and network size. The association between loneliness and mortality was stronger in the studies that used a more representative population. The association between network size and mortality diminished as a result of this grouping.

The next set of NOS-criteria we used in sensitivity analyses regards the duration and adequacy of follow-up. Grouping studies according to duration of follow-up had different effects for loneliness and social network size: the association between loneliness and mortality was stronger with a follow-up of ten years or less, whereas the association between network size and mortality was no longer significant and showed a wider Confidence Interval with a follow-up over 10 years (Table 4).

‘Adequacy of follow-up’ refers to the loss of follow-up of participants and the description of those lost to follow-up. Grouping studies according to this criterion had similar effects in studies with loneliness and studies with network size. The association between loneliness/network size and mortality was stronger when only studies with (near) complete follow-up were regarded.

Additional sensitivity analyses

Because there was some overlap in studies using data from the same group of participants, we repeated our analyses excluding overlapping studies. We only used the results from the most recent studies. The results show that this did not influence the Hazard Ratios: 1.12 (95% CI 1.06–1.17) for the loneliness studies and 0.96 (95% CI 0.94–0.99) for the network size studies. Heterogeneity was not influenced either ($I^2$ statistic for the loneliness studies 76 and for the network size studies 81).

Heterogeneity

Statistical heterogeneity was large. Across the loneliness studies, the $I^2$ statistic was 72, with a Cochran’s Q-test at $0.001$. The same values applied to the network sizes studies: $I^2 = 81$, and $p = 0.001$. Grouping the studies according to covariates and according to NOS-criteria influenced heterogeneity. Network size studies that included depression as a covariate were statistically less heterogeneous. Loneliness studies were less statistically heterogeneous when they included a ‘social contact variable’ as a covariate (Table 4). Grouping the studies according to the NOS-criterion ‘representativeness’ resulted in a less statistically heterogeneous group for the studies that used a selected population, both in loneliness and in network size studies. Grouping studies according to
### A  Meta Analysis

| Study name | Statistics for each study | Hazard ratio and 95% CI |
|------------|---------------------------|------------------------|
|            | Hazard ratio | Low limit | Upper limit | Z-Value | p-Value |
| Aguiar 2020 | 1.290 | 1.146 | 1.469 | 4.035 | 0.000 |
| Conde-Sala 2020 | 1.270 | 1.111 | 1.452 | 3.506 | 0.000 |
| Dragstedt 2012 | 1.040 | 0.997 | 1.085 | 1.881 | 0.069 |
| Ellwardt 2015 | 1.016 | 0.981 | 1.053 | 0.879 | 0.380 |
| Ellervik 2017 | 1.440 | 1.325 | 1.565 | 8.586 | 0.000 |
| Holwerda 2010 | 1.050 | 0.946 | 1.165 | 0.918 | 0.358 |
| Holwerda 2010 | 1.300 | 1.038 | 1.628 | 2.288 | 0.022 |
| Holwerda 2011 | 1.040 | 0.897 | 1.206 | 0.519 | 0.603 |
| Hoogendijk 2020 | 1.060 | 0.920 | 1.221 | 0.609 | 0.418 |
| Iocovich 2011 | 1.120 | 0.022 | 57.247 | 0.056 | 0.955 |
| Julsing 2016 mod | 1.000 | 0.847 | 1.180 | 0.000 | 1.000 |
| Julsing 2016 sev | 1.400 | 0.849 | 2.338 | 1.139 | 0.187 |
| Jylha 1989 | 1.020 | 0.838 | 1.253 | 0.012 | 0.955 |
| Lara 2020 | 1.020 | 0.934 | 1.113 | 0.443 | 0.658 |
| Luo 2014 | 1.040 | 0.916 | 1.085 | 0.100 | 0.965 |
| Ng 2021 m | 1.250 | 0.920 | 1.699 | 1.425 | 0.154 |
| Ng 2021 | 1.400 | 1.052 | 1.863 | 2.267 | 0.021 |
| Novak 2020 | 1.320 | 0.767 | 2.271 | 2.603 | 0.016 |
| Novak 2020 | 1.640 | 0.977 | 2.752 | 1.873 | 0.061 |
| Oliva 2017 | 1.050 | 0.950 | 1.160 | 0.958 | 0.338 |
| Olsen 1991 | 1.140 | 0.965 | 1.347 | 1.540 | 0.124 |
| O’Sullivan 2019 | 1.070 | 0.961 | 1.191 | 0.235 | 0.021 |
| Perlis and 2012 | 1.460 | 1.114 | 1.887 | 2.764 | 0.006 |
| Schutter 2020 | 1.960 | 0.988 | 1.937 | 1.619 | 0.105 |
| Stefke 2012 | 0.930 | 0.785 | 1.102 | -0.439 | 0.632 |
| Steensma 2014 | 0.940 | 0.558 | 1.565 | -0.635 | 0.424 |
| Sugisawa 1994 | 1.022 | 0.032 | 32.672 | 0.012 | 0.999 |
| Tabue Teguo 2016 | 0.940 | 0.032 | 32.672 | 0.012 | 0.999 |
| Tanskanen 2016 | 1.052 | 1.052 | 1.052 | 1.052 | 1.052 |
| Tanskanen 2016 | 1.170 | 1.021 | 1.341 | 2.257 | 0.024 |
| Wang 2020 | 1.000 | 0.756 | 1.323 | 0.000 | 1.000 |
| Youm 2021 | 1.320 | 0.832 | 1.477 | 2.238 | 0.018 |
| Youm 2021 | 1.101 | 1.059 | 1.144 | 0.662 | 0.790 |

#### Meta Analysis

M male; F female; mod moderate; sev severe

### B  Meta Analysis

| Study name | Statistics for each study | Hazard ratio and 95% CI |
|------------|---------------------------|------------------------|
|            | Hazard ratio | Low limit | Upper limit | Z-Value | p-Value |
| li et al. 2018 | 1.010 | 1.000 | 1.020 | 1.970 | 0.049 |
| Cerhan 1997 | 0.670 | 0.412 | 1.089 | -1.615 | 0.106 |
| De Brito 2017 | 0.580 | 0.350 | 0.961 | -2.114 | 0.035 |
| Ellwardt 2014 | 0.990 | 0.982 | 0.998 | -2.438 | 0.015 |
| Giles 2005 | 0.950 | 0.911 | 0.991 | -2.389 | 0.017 |
| McLaughlin 2011 | 0.890 | 0.837 | 0.946 | -3.731 | 0.000 |
| Roth 2020 | 0.900 | 0.814 | 0.995 | -2.058 | 0.040 |
| Schutter 2020 | 0.840 | 0.663 | 1.065 | -1.443 | 0.149 |
| Shye 1995 | 0.670 | 0.422 | 1.064 | -1.698 | 0.090 |
| Vogt 1992 | 0.500 | 0.255 | 0.981 | -2.017 | 0.044 |
| | 0.960 | 0.933 | 0.989 | -2.164 | 0.074 |

#### Meta Analysis

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**Fig. 2**  Forest plots showing the results for studies studying the association between mortality and loneliness (A) and between mortality and network size (B)
follow-up duration had comparable effects on heterogeneity in loneliness and network size studies. Grouping according to ‘adequacy of follow-up’ however only had an effect on loneliness studies: with higher loss to follow-up, studies appeared to be less heterogeneous. We also investigated the effect of ‘outliers’: in the forest plot (Fig. 2A) showing the association between loneliness and mortality, two studies show very large Confidence Intervals. Removing these studies from the analysis did not diminish heterogeneity: $I^2 = 74, p < 0.001$, nor did it effect Hazard Ratio: $1.10, 95\% \text{CI} 1.06–1.15$. The same procedure was followed for investigating the effect of different sample sizes: removing smaller studies (~1000 participants) did not diminish heterogeneity in the loneliness studies: $I^2 = 79, p < 0.001$, nor in the network size studies: $I^2 = 84, p < 0.001$. Additionally, we examined the effect of the assessment of loneliness on heterogeneity by including only studies that used a questionnaire. This diminished heterogeneity somewhat: $I^2 = 46, p = 0.03$, while also diminishing the Hazard Ratio ($1.06, 95\% \text{CI} 1.06–1.10$). Including only studies that assessed loneliness by asking a single question did not reduce heterogeneity: $I^2 = 81, p < 0.001$, with a Hazard Ratio of $1.14 (95\% \text{CI} 1.05–1.24)$. We also examined the effect of excluding studies that were scored on the NOS as of ‘poor quality’. When these studies were excluded, heterogeneity did not diminish: $I^2 = 79, p < 0.001$, while the Hazard Ratio was $1.08 (95\% \text{CI} 1.04–1.13)$.

**Publication bias**

The funnel plots (Fig. 3) show a fairly symmetrical distribution of loneliness studies (A), but a one-sided distribution of network size studies (B). Therefore, publication of studies investigating the association between network size and mortality could be biased in the direction of showing a stronger association than actually present.
Discussion

This meta-analysis was performed to investigate whether loneliness and social network size in older adults are associated with mortality and to accumulate evidence for either the subjective aspects or the objective aspects of missing social relationships to be more important in this association. Additionally, the role of important covariables such as depression was investigated.

In the present study, both loneliness and small network size show an association with mortality in older adults. These results are in line with previous meta-analyses investigating mortality effects of loneliness, social isolation and social relationships (Holt-Lunstad et al. 2010, 2015; Rico-Uribe et al. 2018). Compared with the present study, these meta-analyses showed larger effect sizes, varying from a Hazard Ratio of 1.22 (Rico-Uribe et al. 2018) to an Odds Ratio of 1.50 (Holt-Lunstad et al. 2010). In comparison, in a study by Katzmarzyk et al. (2003) the Relative Risk of
all-cause mortality for elevated Body Mass Index was 1.23 (95% CI 1.18–1.29) and for physical activity 0.80 (95% CI 0.78–0.82).

In order to compare the associations with mortality of loneliness and social network size it is essential that studies investigating the associations between loneliness and mortality control for social network size and vice versa. Of the studies investigating the associations between loneliness and mortality that were included, more than half controlled for a social contact variable, although in only three studies this variable was the actual size of the social network. These studies still showed an association between loneliness and mortality (Table 4). Therefore, it can be concluded that loneliness in itself is associated with higher mortality, independent of the objective social situation. Unfortunately, the studies in this meta-analysis investigating the association between mortality and social network size did not control for feelings of loneliness. As a consequence, the effects of loneliness and social network size cannot be compared directly. Only two studies investigated both loneliness and social network size (Ellwardt et al. 2015; Schutter et al. 2020). One of these studies concluded that social network size was associated with mortality, but loneliness was not (Ellwardt et al. 2015); the other study concluded that neither was associated with mortality (Schutter et al. 2020).

With respect to covariables, we investigated the role of depression. Studies in the present meta-analysis that included depression as a covariate still showed a significant association with mortality. In accordance with our results, sensitivity analyses in the meta-analysis by Rico-Uribe et al. (2018) showed that when only studies were included that used depression as a covariate, loneliness was still associated with higher mortality. These findings suggest that loneliness and small social network size might be risk factors for mortality in themselves, irrespective of depression.

Contrary to the present study, Holt-Lunstad et al. (2010; 2015) included unadjusted mortality risks and concluded that the number of covariables included was negatively associated with effect size (Holt-Lunstad et al. 2015). The difference in effect size between unadjusted Hazard Ratios and fully adjusted Hazard Ratios reached statistical significance (Holt-Lunstad et al. 2015). This could partly explain the smaller Hazard Ratios in the present meta-analysis, since we only included studies that adjusted for a number of relevant covariables. In addition, the three previous meta-analyses (Holt-Lunstad et al. 2010, 2015; Rico-Uribe et al. 2018) were done on studies including also younger participants. It is conceivable that the effects of loneliness and social network size on mortality are smaller in older versus younger people. This is illustrated by a number of studies in the present analysis that investigated the association between loneliness and mortality in older adults over the age of 70 years: 6 out of 8 studies did not find a significant association (Table 2). Furthermore, smaller associations between loneliness and mortality were found when only the studies that followed participants for more than 10 years were included in the meta-analysis (Table 4). Apparently, when people grow older, other factors can become more important. This is in accordance with the results in the meta-analyses by Holt-Lunstad et al. (2015). They included adults aged under 50 to over 80 years and concluded that the effects of loneliness and social isolation on mortality risk diminished with age. Similarly, Lara et al. (2020) analyzed different age groups and found that loneliness was associated with mortality in younger and middle-aged adults, but not in older adults. Unfortunately, the effect of age has not been examined in the study by Rico-Uribe et al. (2018).

The large statistical heterogeneity between the included studies obviously influences the external validity. We tried to explain heterogeneity by adding sensitivity analyses, but these did not provide a sufficient explanation. One of the aspects that could underlie this heterogeneity is the fact that the range of loneliness prevalence is large, especially in the studies that were published before 2018: this range is 6–43% (Standard Deviation (SD) 12.5), whereas in the studies published after 2017 this range is 23–36% (SD 5.2). Other aspects are the age of included participants (≥ 60 versus ≥ 70) and the representativeness of the study population: some studies included a nationally representative population, whereas other studies included only urban or only rural populations. These aspects comprise clinical heterogeneity, which compromises generalizability to broader populations. Other aspects of heterogeneity can be described as methodological heterogeneity, such as differences in follow-up or the introduction or omitting of covariables (Deeks et al. 2008). The grouping of studies according to covariables and NOS-criteria resulted in lower heterogeneity for some groups. For example, including only loneliness studies that included a social contact variable resulted in little heterogeneity ($I^2$<40), while diminishing but not annihilating the Hazard Ratio. Moderate heterogeneity was reached in the loneliness studies when depression was not included as a covariate, and in the network size studies when depression was included. Again, the Hazard Ratios were influenced but remained elevated. The finding that the Hazard Ratios remained significantly elevated in less heterogeneous groups of studies might signify that loneliness and social network size are associated with mortality, although other variables are of influence. Gender differences might also explain heterogeneity. However, since only three studies provided separate outcomes for men and women, we did not perform additional sensitivity analyses with gender. In their meta-analysis, Rico-Uribe et al. (2018) divided studies...
by gender and concluded that for both men and women, there was a significant association between loneliness and mortality, with a slightly higher Effect Size for men. A recent study by Lennartsson et al. (2021) examined gender differences in the association between mortality and both loneliness and social isolation. They concluded that there were small differences: the association between loneliness and mortality was stronger in men, whereas the association between social isolation and mortality was stronger in women. However, this is only partly comparable to the studies in our meta-analysis, since they did not use social network size as a measure for social isolation but a social isolation index. The three studies in our meta-analysis that analyzed men and women separately showed various outcomes (see Fig. 2A).

The results of this meta-analysis have implications for both clinical practice and public health. For clinicians working with older patients, inquiring after the existence of loneliness or social isolation should be as common as inquiring after smoking, alcohol use or physical exercise, since the effects on mortality of loneliness and social isolation can be as deadly (Holt-Lunstad et al. 2010; House et al. 1988). Additionally, addressing loneliness and social isolation should be on the agenda of public health institutions. Local and national initiatives to combat loneliness and social isolation should be supported by governments. The relevance of these measures has recently been emphasized by studies showing heightened loneliness and social isolation in older adults as a consequence of the COVID-19 pandemic (Cudjoe et al. 2020; Kotwal et al. 2020).

The strengths of our study are that this is the first meta-analysis that included only older adults and that the quality of most of the included studies is good, based on the NOS-scores. An additional strength is the performance of sensitivity analyses to try to unravel the effects of different variables on the associations of loneliness and social network size with mortality. It should also be mentioned that studies that did not control for covariates were excluded, leading to more comparable studies. Furthermore, we were able to execute a comprehensive systematic search, and studies were selected by independent authors. Since an association between loneliness/network size and mortality was found in studies using cohorts that were representative for older adults in the community, our results may be relevant for the general public and for public health. Finally, although only studies in English were included, we were able to include not only studies from the Western world, but also from Brazil, China, Japan, Singapore and South Korea.

There are some limitations to this study too. Firstly, heterogeneity was large and could only partly be accounted for by grouping studies according to covariates, NOS-criteria, sample size and method of measuring loneliness. Large heterogeneity compromises generalizability to a broader population. Secondly, as our study involved merely observational longitudinal studies, causality cannot be assessed. Thirdly, since loneliness and social network size were measured at only one time point in the studies included, variance and persistence of loneliness have not been taken into account. Finally, the funnel plot showed that there is a possible publication bias regarding studies on network size, since only positive studies were published.

Conclusion
In conclusion, this meta-analysis shows that both loneliness and a small social network are associated with a small mortality risk in older adults, which appears to decrease over time. This risk is not influenced by the presence of depression. Since both subjective and objective aspects of social contacts appear to be relevant, interventions should be aimed both at the subjective experience of social contacts as well as the expansion of the size of the network. In addition, as a consequence of the fact that we included mostly epidemiological studies, there are important implications for public health. Targeting subjective and objective aspects of older adults’ social contacts should be on the agenda of preventive as well as personalized medicine. Finally, in order to gather evidence for either the objective or the subjective lack of social contacts to pose the greater mortality risk, more comparative studies need to be done.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are of relevance to the content of this article.

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