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The Relationship between Loneliness and Health

A literature review

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Foreword

This literature review is part of a broader series of activities that will take place in 2021-2023 in the context of a European Parliament pilot project on monitoring loneliness in Europe. The European Commission Directorate-General for Employment, Social Affairs & Inclusion (DG EMPL), in collaboration with the Joint Research Centre (JRC), will carry out a number of tasks including the collection of pan-European data on loneliness, a review of existing literature and identification of knowledge gaps, and the establishment of a web platform to monitor loneliness over time and across Europe.

For more material and information, please visit the webpage https://knowledge4policy.ec.europa.eu/projects-activities/loneliness-european-union_en

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Executive Summary

The **link between loneliness and health** has been extensively documented in scientific literature. Loneliness is widely recognized as being a public health issue and concern has been heightened during the COVID-19 pandemic. A clear understanding of the association between loneliness and mortality and morbidity is needed to judge the extent of loneliness as a public health challenge and the need for interventions. This report summarizes evidence from the emerging academic literature on the topic, addresses the potential mechanisms linking loneliness and health, as well as the concerns related to the presence of reverse causality.

The collected evidence can be summarized as follows:

- **Loneliness**, in particular chronic loneliness, **is associated with a higher mortality risk and a higher risk of adverse health conditions**. This includes risks to **physical health** (cardiovascular disease, high blood pressure, stroke, functional decline, diabetes), **cognitive function** (dementia and Alzheimer's disease), and **mental problems** (depression, anxiety, suicidal thoughts and behaviours, and depressive symptoms such as lack of interest, lack of concentration, inability to take pleasure from normal activities and a tendency to cry).
- Several **potential mechanisms** have been proposed to explain the association between loneliness and health. Being lonely is associated with developing unhealthier lifestyles, worse sleep quality, and higher levels of stress, which are known health risk factors. Furthermore, loneliness influences biological markers of health; notably, it is related to a dysregulation of the neuroendocrine (hormonal) system and systemic inflammation. Moreover, some of the health conditions associated with loneliness can in turn cause other health problems. This includes depression and anxiety, closely linked to neuroendocrinal dysregulation and cardiovascular disease, which can promote dementia by affecting blood vessels in the brain.
- There is also a **reverse relationship: some health conditions, particularly those that make individuals less likely to connect with others, are associated with an increased risk of becoming lonely**. These include depression and anxiety; poor physical health, especially disability and hearing loss; and potentially cognitive impairment.

1. Introduction

Loneliness is the state of perceived social isolation, with the feeling that either the quality or quantity of one's social interactions is insufficient (Perlman and Peplau, 1984). This definition implies that loneliness is subjective and distinct from objective social isolation; it is possible to feel lonely in a crowd and to be alone without feeling lonely (Perlman and Peplau, 1984). Loneliness can be a transient feeling or become chronic. In particular, when it is severe and chronic, loneliness is a profoundly painful experience and a "debilitating psychological condition characterized by a deep sense of emptiness, worthlessness, lack of control, and personal threat" (Cacioppo, Hawkley and Thisted, 2010).

Most of us feel lonely sometimes, and for many, it becomes a constant feeling. According to data from the European Quality of Life Survey, around 12% of EU citizens felt lonely more than half of the time in 2016 (Baarck et al., 2021). There is inconclusive evidence on the distribution of loneliness across age groups. Some studies find an elevated incidence of loneliness in adolescence and at the oldest age (Victor and Yang, 2012; Lasgaard, Friis and Shevlin, 2016). Others find that loneliness is monotonically increasing (Yang and Victor, 2011) or decreasing (Beutel *et al.*, 2017) with age. Recent evidence suggests three peaks in the occurrence of loneliness across the life course: one in adolescence or young adulthood, one at old age, and an additional peak at around 50-60 years of age (Luhmann and Hawkley, 2016; Hawkley *et al.*, 2022). The higher incidence of loneliness among older individuals may thus become a larger concern in the context of rapid population ageing in many countries.

Recently, the prevalence of loneliness has been affected by the COVID-19 pandemic and the associated contact restrictions, such that the number of EU citizens feeling lonely more than half of the time has doubled to 25% (Baarck *et al.*, 2021). Overall, the evolution of loneliness in industrialized countries over the last decades is not clear, with studies finding conflicting evidence. Among young adults, newer evidence indicates increasing levels of loneliness (Buecker *et al.*, 2021). Among older European individuals, loneliness levels are generally found to be constant (Dykstra, 2009; Dahlberg, Agahi and Lennartsson, 2018; Buecker *et al.*, 2021).

Loneliness is increasingly been viewed as a public health problem (Buecker *et al.*, 2021), due to evidence linking it with negative health outcomes and mortality (for general reviews, see Hawkley and Cacioppo, 2010; Cacioppo, Capitanio and Cacioppo, 2014; Ong,

Uchino and Wethington, 2016; Leigh-Hunt *et al.*, 2017; National Academies of Sciences, Engineering, and Medicine, 2020), with newspapers publishing headlines such as "Loneliness is a serious public-health problem" (The Economist, 2018), "Let's Wage a War on Loneliness" in the New York Times (Kristof, 2019); and "Millennials And The Loneliness Epidemic" in Forbes (Howe, 2019). Another concern is that loneliness is a social and civic problem: lonely individuals tend to be more hostile and less trusting, which may erode cohesion in society (Cuccu and Stepanova, 2021). Loneliness is also more prevalent among poorer individuals (Baarck *et al.*, 2021), which places an additional burden on those who already face higher health risks and higher barriers to accessing health care (Murray, 2006; World Bank, 2014). In response, several countries run campaigns to reduce loneliness (The Economist, 2018), the US surgeon general has made loneliness a priority (Murthy, 2020); and the UK and Japan have established ministers for loneliness in 2018 and 2021, respectively (Department for Digital, Culture, Media & Sport, Office for Civil Society, 2021).

A clear understanding of the association between loneliness and mortality and morbidity is needed to judge the extent of loneliness as a public health challenge and the need for interventions. This report summarizes evidence from the academic literature on the link between loneliness and health. It strives to collect the current state of the art related to the following queries: Is loneliness associated with worse health outcomes? What are the mechanisms by which this may happen? And conversely, can being in bad health impact social connection and loneliness? Overall, the collected evidence can be summarized as follows:

- Loneliness, in particular chronic loneliness, is associated with a higher mortality risk and a higher risk of negative health consequences. This includes risks to physical health (cardiovascular disease, high blood pressure, stroke, functional decline, diabetes), cognitive function (dementia and Alzheimer's disease), and mental health (depression, anxiety, suicidal thoughts and behaviours, and depressive symptoms such as lack of interest, lack of concentration, inability to take pleasure from normal activities and a tendency to cry).
- Several potential mechanisms have been proposed to explain the association between loneliness and health. Being lonely is associated with developing unhealthier lifestyles, worse sleep quality, and higher levels of stress, which are known health risk factors. Furthermore, loneliness influences biological markers

of health; notably, it is related to a dysregulation of the neuroendocrine (i.e., hormonal) system and systemic inflammation. Moreover, some of the health conditions associated with loneliness can in turn cause other health problems. This includes depression and anxiety, which have been linked to neuroendocrinal dysregulation and cardiovascular disease, which can promote dementia by affecting blood vessels in the brain.

- There is also a reverse relationship: some health conditions, particularly those that make individuals less likely to connect with others, are associated with an increased risk of becoming lonely. This includes depression and anxiety; poor physical health, especially disability and hearing loss; and potentially cognitive impairment.

Most of the reported studies reveal correlations that can say little about causation. Based on the existing evidence, we are able to say that lonely individuals have, for instance, higher blood pressure than their non-lonely peers (cross-sectional study) or that participants who are lonelier at the outset of the study have a higher risk of having developed elevated blood pressure a few years later (longitudinal or prospective study). This is different from saying that loneliness causes high blood pressure. Moreover, it is often impossible to tell apart the direction of the connection, *i.e.*, whether the observed effect quantifies the impact of loneliness on health or vice versa (reverse causality).

The rest of the document is organized as follows. Section 2 presents the existing evidence on the association between loneliness and different health outcomes. Section 3 describes the potential mechanisms, while Section 4 briefly reviews the reverse relationship, summarizing the ways in which health may be linked to a higher risk of developing loneliness. Section 5 concludes.

2. Is loneliness associated with worse health?

Loneliness is significantly correlated with increased mortality and a higher prevalence of several morbidities, including cardiovascular disease, functional decline, cognitive decline, dementia, depression, and suicidal behaviour. There is also some evidence that loneliness is associated with reduced immunity, diabetes and anxiety. Further evidence suggests that some health outcomes may be related to loneliness in a *dose-response* relationship, meaning that the higher the level or longer the exposure to loneliness, the

stronger the effect on health. In what follows, we summarize the main findings linking loneliness to overall mortality, physical health, cognitive functioning, and mental health.

Mortality

Loneliness and other aspects of social connection are emerging as potential risk factors for mortality. The existing research has focused on both *all-cause* mortality and *cause-specific* mortality, in particular mortality related to cardiovascular disease and stroke. All-cause mortality risk of loneliness can be interpreted as the cumulated death risk of all conditions related to loneliness, while cause-specific mortality risk of loneliness evaluates the risk of dying from a specific morbidity closely related to loneliness.

Existing evidence suggests that lonely individuals face lower odds of survival. The risk gradient attributable to loneliness is similar to the one related to obesity and comparable to other well-established risk factors such as environmental quality and physical activity (Holt-Lunstad *et al.*, 2015). More precisely, two recent meta-analyses find that loneliness increases the risk of all-cause mortality by 22% (Rico-Uribe *et al.*, 2018) and 26% (Holt-Lunstad *et al.*, 2015). Furthermore, these findings were consistent across age, gender, cause of death, country of origin, and initial health status. Several other studies and meta-analyses have replicated these findings (Shiovitz-Ezra and Ayalon, 2010; Luo *et al.*, 2012; Tanskanen and Anttila, 2016).

In an influential longitudinal study, Perissinotto et al. (2012) find that loneliness is associated with a 45% higher risk of mortality among individuals aged 60 years or older, even after controlling for demographic and socio-economic characteristics, health status, and the presence of depressive symptoms. In a similar vein, Elovainio et al. (2017) confirm that lonely individuals have a higher mortality risk. However, the effect of loneliness becomes insignificant when additional biological, behavioural, socioeconomic, and psychological mortality risk factors are taken into account. This result might suggest that loneliness is not independent of the other mortality risk correlates and that the observed effect of loneliness on the increased odds of dying passes through these additional confounding factors.

Some studies attempt to untangle the separate contributions of loneliness and social isolation (the objective measure of the quantity of social contacts) to excess mortality risk. While many studies have considered the effect of loneliness or social isolation on

mortality separately and generally found that both are related to higher mortality risk, only a few have included both factors at once. It appears that when including loneliness and social isolation, only social isolation is a significant predictor of mortality, and loneliness becomes irrelevant (Steptoe *et al.*, 2013; Elovainio *et al.*, 2017). This result may suggest that social isolation is the underlying factor that influences both mortality and loneliness. Indeed, Steptoe et al. (2013) find that when evaluated separately, mortality risk is higher among socially isolated and lonely participants, controlling for demographic, socio-economic, and health factors. However, when considered jointly, only social isolation significantly correlates with mortality. Similar results have been found by Elovainio et al. (2017). Finally, in a cross-sectional study, Beller and Wagner (2018) suggest that loneliness and social isolation act synergistically on mortality, such that higher levels of one factor amplify the effect of the other.

To summarize, loneliness is significantly associated with an increased mortality risk. The mechanisms of this connection may include increased morbidity among lonely individuals, as laid out in the next part. When comparing loneliness and social isolation as risk factors for mortality, limited evidence suggests that social isolation is the more important factor.

Physical health

In addition to the evidence linking loneliness and social isolation with mortality, other research has established that loneliness significantly correlates with specific health conditions, in particular cardiovascular diseases, stroke, and functional decline. There is also some evidence that lonely individuals suffer more from decreased immune function and diabetes.

Cardiovascular disease

Coronary heart disease (which includes heart attacks) and stroke represent two major causes of death in the world, and they are among the top three greatest causes of death for high-income countries (World Health Organization, 2019). Both conditions can be summarized under the umbrella term cardiovascular disease (CVD henceforth), which includes diseases related to the heart or blood vessels. Loneliness is associated with an increased risk of developing stroke and coronary heart disease, including heart attack (acute myocardial infarction), among middle-aged and older individuals (Hakulinen *et*

al., 2018; Valtorta *et al.*, 2018; Casabianca and Kovacic, 2022).[1] A meta-analysis conducted by Valtorta et al. (2016) based on 23 different studies performed on 16 longitudinal data sets shows that loneliness and social isolation are associated with a 29% increase in the risk of coronary heart disease and a 32% increase in the risk of stroke, for both genders and independent of traditional heart disease risk factors.

Loneliness is also associated with a higher risk of developing high blood pressure among middle aged and older adults (Hawkley *et al.*, 2010). Similarly, meta-analyses indicate that loneliness is associated with higher blood pressure and inflammatory reactivity (Brown, Gallagher and Creaven, 2018). Several other studies reached similar results. For instance, Casabianca and Kovacic (2022) report that loneliness directly increases the probability of high blood pressure by 12%. Focusing on young individuals, Caspi et al. (2006) analyse how social isolation and loneliness during childhood and adolescence up to age 26 affects cardiovascular disease risk in young adulthood. In that paper, a participant is classified as at risk for heart disease if at least 3 out of 6 biomarkers apply (overweight, elevated blood pressure, elevated total cholesterol level, low high-density lipoprotein level, elevated glycated haemoglobin concentration, and low maximum oxygen consumption). Being lonely in adolescence increases the probability of being at risk of heart disease by 26%, when controlling for multiple other risk factors.

Some studies compare the relative importance of loneliness and social isolation for the risk of CVD by including both factors at once. Valtorta et al. (2018) find that loneliness but not social isolation is associated with an increased risk of coronary heart disease and stroke, controlling for demographic, socio-economic, and cardiovascular health factors. In Hakulinen et al. (2018), both loneliness and social isolation are correlated with an increased risk of coronary heart disease and stroke when minimally adjusting only for demographics.

Loneliness may be associated in a dose-response or cumulative relationship with CVD. This means that the risk of developing CVD is higher the higher the level of or the longer the exposure to loneliness. The evidence on this is mixed with differences between CVD

[1] However, for Hakulinen et al. (2018), this holds only for the simple model with demographic and socioeconomic controls. whereas for Valtorta (2018), it holds for the full model, including a battery of traditional CVD risk factors. In the full model of Hakulinen et al. (2018) with biological and behavioural factors, depressive symptoms, and chronic disease, the association between loneliness and CVD becomes insignificant.

on the one hand and its risk factors on the other hand. In Hawkley et al. (2010) higher initial levels of loneliness are associated with greater increases in systolic blood pressure, pointing to a dose-response relationship. Furthermore, in the study by Caspi et al. (2006) on young individuals, the higher the number of occasions when the participants are isolated or lonely (*i.e.,* childhood, adolescence, 26 years old), the higher the risk of heart disease, suggesting a cumulative relationship. On the other hand, Valtorta et al. (2018) does not find a cumulative relationship between loneliness and coronary heart disease or stroke, when considering the number of waves during the follow-up for which the participants felt lonely.

Functional and motor decline

Functional decline is described as the loss of an individual's ability to independently and safely perform activities of daily living (ADL), such as bathing, dressing, and eating at a basic level, and shopping, driving, and banking at a higher level (Beaton and Grimmer, 2013). Motor decline, on the other hand, refers to a loss of the ability to execute activities or movements using motor neurons.

Loneliness is both associated with a stronger functional and motor decline. A longitudinal study by Perissinotto et al. (2012) reports a stronger functional and motor decline in lonely individuals compared to their non-lonely counterparts for activities of daily living (ADL), upper extremity tasks, mobility and stair climbing, while controlling for demographic, socioeconomic and medical factors. Lonely individuals also display a higher motor decline measured by muscle strength and motor performances such as time to walk a certain distance or stand on one leg (Buchman *et al.*, 2010). Participants scoring 1 point higher on the 0-5 loneliness scale at study onset would exhibit a 40% more rapid annual rate of motor decline, when controlling however only for sociodemographic factors. This is equivalent to being 4 years older at baseline. The association between loneliness and motor decline stays significant when additionally controlling for social isolation. Along similar lines, Casabianca and Kovacic (2022) reveal that gradual increase in loneliness translates into 0.45 more limitations in ADL.

Except for a very limited number of studies, it is not clear whether loneliness affects functional decline indirectly through other processes such as cardiovascular diseases or inflammation, which contribute to motor decline, or rather directly. For example, lone-

liness is associated with poor self-regulation (executive control), which may lead to decreased exercise or changes in eating habits, and in turn to motor decline (Buchman *et al.*, 2010).

Diabetes and cholesterol

A limited number of studies link loneliness to diabetes. Lukaschek et al. (2017) find a positive association between loneliness and the risk of developing diabetes only for men.[2] A cross-sectional study by Richard et al. (2017) reports that lonely individuals are 40 percent more likely to have diabetes and 31 percent more likely to have high cholesterol levels.

Immunity

As reported in a small number of studies, immunity may be suppressed among lonely individuals in some contexts. In addition, lonely individuals may feel worse when they are ill than their non-lonely counterparts. Lonely university students display a poorer immune response to an influenza vaccine, developing fewer antibodies than non-lonely participants (Pressman *et al.*, 2005). In a research conducted by Leroy et al. (2017), study participants first reported their level of loneliness and were then infected with a common cold virus and observed for several days. Lonely participants were no more likely to develop a cold, and their objective cold symptoms (mucus weight) were of similar severity. However, lonely participants felt more severe subjective symptoms of a cold, controlling for demographics, depression, and season of participation.

Cognitive Function

Cognitive function is a large set of mental processes that allow a person to acquire knowledge, to reason, and to make and execute plans. These include perception, memory, learning, attention, decision-making, and language abilities (Kiely, 2014). Dementia is a clinical condition characterized by loss of cognitive function, including "increasing loss of memory, confusion, and personality changes, as well as problems with verbal or written expression, spatial orientation, and other everyday activities" (Shankar *et al.*, 2013). Alzheimer's disease is the most common form of dementia.

[2] Here, loneliness is conceptualized as low satisfaction with social networks.

Cognitive decline

Several studies have examined the associations between loneliness and/or social isolation with the risk of cognitive decline in older adults. Loneliness is generally found to be associated with a higher risk of experiencing cognitive decline (Cacioppo and Hawkley, 2009). However, studies disagree on which part of cognitive function is affected. In a cross-sectional setting, lonely individuals display lower cognitive function as measured by a global measure of cognition, several memory types (episodic, working, semantic), perceptual speed, as well as visuospatial ability, when controlling for socio-demographic factors (Wilson *et al.*, 2007). In the longitudinal part of the research,[3] lonely individuals experienced a stronger decline over the follow-up period for all of the above cognitive functions except episodic and working memory. Shankar et al. (2013) measure cognitive function by verbal fluency ("name as many animals as possible in one minute"), as well as immediate and delayed recall ("remember a list of 10 words, reproduce them directly and after an interval"). Lonely participants saw a stronger decrease in immediate and delayed recall than non-lonely participants, but no difference in verbal fluency. Finally, a meta-analysis with eight studies on the subject groups loneliness along with social support and satisfaction with household members as a functional measure of social relationships (Kuiper *et al.*, 2016). Low scores on this combined functional measure of social relationships are associated with a higher risk of cognitive decline.

Dementia and Alzheimer's

Most evidence indicates that loneliness and perceived quality of relationships are positively correlated with the risk of developing dementia, including Alzheimer's disease (Wilson *et al.*, 2007; Amieva *et al.*, 2010; Holwerda *et al.*, 2014; Kuiper *et al.*, 2015; Rafnsson *et al.*, 2020). The size of this association is comparable to that of other well-established dementia risk factors such as physical inactivity, low education, and late-life depression (Kuiper *et al.*, 2016).

A meta-analysis including four research articles on the subject finds that loneliness is not significantly associated with a higher risk of dementia (Penninkilampi *et al.*, 2018). Conversely, the two more recent studies included in the meta-analysis observe a positive association between loneliness and dementia risk (Wilson *et al.*, 2007; Holwerda *et al.*,

[3] Longitudinal studies are based on samples of initially dementia-free participants and observe the development of cognitive function over the follow-up period.

2014). The previously mentioned study by Wilson et al. (2007) finds that the risk of clinical Alzheimer's disease over a follow-up of 4 years increases by 51% for each additional point on the 5-point loneliness scale, controlling for sociodemographic factors. Similarly, Holwerda et al. (2014) show that lonely individuals were 1.64 times more likely to develop clinical dementia over three years than their non-lonely counterparts, after controlling for demographics, medical factors, depression and social isolation. Finally, Rafnsson et al. (2020) document that dementia risk increases by 44% for each additional point on a 3-point loneliness scale, independent of demographics, health factors, and depression. Furthermore, the authors try to address the potential problem of reverse causality, *i.e.*, individuals in the early stages of dementia may have more difficulty engaging in and keeping up social relationships, and therefore feel lonely because of dementia (and not the other way around). To counter this concern, generally, participants with diagnosed dementia at the beginning of the study period are excluded. Here, the authors go further and exclude dementia cases that appeared in the first 24-48 months after the initial loneliness assessment and still find that loneliness predicts a similar increase in dementia risk.

Mental Health

A wide literature has established a significant relationship between loneliness and several mental health disorders, including depression, anxiety, personality disorders, psychosis, and suicidal ideation. In what follows, we report the main findings related to the most explored manifestations of mental problems, namely depression, anxiety, and suicidality.

Depression and Anxiety

Depression and anxiety are among the most common mental health disorders affecting older adults (Domènech-Abella *et al.*, 2019). Most cross-sectional studies show that loneliness is positively associated with the prevalence of depressive symptoms and anxiety (Choi, Irwin and Cho, 2015), regardless of age, sex, partnership, and socioeconomic status (Beutel *et al.*, 2017).

A growing body of research has employed validated instruments for measuring loneliness and has found positive associations between loneliness and depression and anxiety over time. Several longitudinal studies show that a higher initial level of loneliness is

associated with an increased risk of developing anxiety (Domènech-Abella *et al.*, 2019) and depression (Cacioppo, Hawkley and Thisted, 2010; Luo *et al.*, 2012; Jeuring *et al.*, 2018; Domènech-Abella *et al.*, 2019) during the follow-up, controlling among others for initial levels of depression. These results hold for different age groups (middle-aged and older adults) and control variables, including the initial existence of depression or anxiety as well as demographics, psychological factors, health status, and social isolation (Domènech-Abella *et al.*, 2019; Cacioppo, Hawkley and Thisted, 2010). Moreover, older adults with late-life depression show a poorer prognosis if they are lonely, controlling for health and depression-related factors but not demographics (Jeuring *et al.*, 2018).

Finally, in an experimental setting, Cacioppo et al. (2006) induce feelings of loneliness among participants using hypnosis. Individuals induced to feel high compared to individuals induced to feel low loneliness reported significantly greater negative mood, anxiety, and anger and significantly less optimism, self-esteem, and social support.

Suicide and Suicidal Ideation

Suicide and suicidal ideation are an important public health issue as well as a devastating experience for individuals, families, and communities. Every year, more than 700,000 people die from suicide worldwide (World Health Organization, 2021).

Loneliness, however, is not an established risk factor for suicidality. Indeed, a recent meta-analysis on the predictors of suicidal thoughts and behaviours based on 365 studies states that the field is still in an exploratory phase with no strong predictors yet isolated (Franklin *et al.*, 2017). In one longitudinal study (Bennardi et al., 2019), loneliness is associated with a higher risk of suicidal ideation among those 60 years and older but not among those 18-59 years old. However, although the association is significant, it is very weak.

Nevertheless, several cross-sectional and interview studies evidence that suicidal ideation and/or suicide attempts often occur concurrently with loneliness (Mezuk *et al.*, 2014; Chang, Chan and Yip, 2017; Heuser and Howe, 2019; Troya *et al.*, 2019). Furthermore, in interviews, loneliness is sometimes given as a reason for suicide attempts and suicidal ideation. For example, van Wijngaarden et al. (2015) interviewed 25 participants over 70 years of age who expressed a death wish and felt that life was completed and no longer worth living. All participants report a sense of aching loneliness, a distance

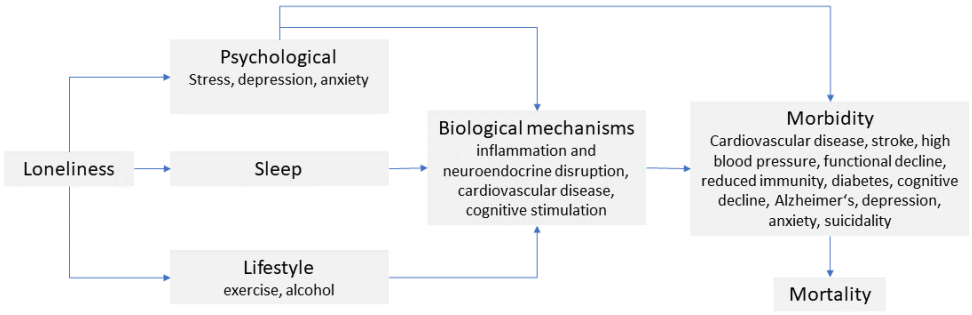
from others, a lack of valuable relationships and companionship. In another study, interviews with 103 older adults who are in hospital after a suicide attempt show that they have higher feelings of loneliness than a control group with similar demographics, with 60% compared to 18% feeling lonely (Wiktorsson *et al.*, 2010). When asking 101 of the same suicide attempters for their reasons, 13 of them named thwarted belongingness or family conflict (Van Orden *et al.*, 2015). This includes several who cite loneliness directly in phrases such as “I don't want to live on my own anymore, I feel so lonely” or “I have lived my life, I am lonely” or “I have no one to talk to”. Furthermore, those who report thwarted belongingness use more lethal methods and are more likely to reattempt suicide during the 12-month follow-up than those giving other reasons.

To summarize, lonely individuals experience higher levels of depression, anxiety, and suicidal ideation than their non-lonely counterparts (Beutel *et al.*, 2017). Furthermore, loneliness is robustly associated with a higher risk of developing depression, and there is also some evidence for a higher risk of anxiety, suicidal behaviour, and other symptoms of depression like lack of interest, lack of concentration, inability to take pleasure from normal activities and a tendency to cry. Furthermore, in interviews with suicide survivors, a portion of respondents cite loneliness as a reason for considering or attempting suicide.

3. Mechanisms linking loneliness to health

The previous section presented evidence that loneliness is associated with a higher risk of mortality and morbidity, including cardiovascular disease, functional decline, diabetes, cognitive decline, dementia, depression, and suicidal ideas and behaviour, as well as potentially decrease immune function and anxiety. Some of this, particularly the potential effect of loneliness on mental health problems, makes intuitive sense. But why should loneliness have a relationship with, say, cardiovascular disease or cognitive function? This section presents the potential mechanisms through which loneliness may affect health: these include unhealthy lifestyles, worse sleep quality, higher levels of stress, depression, and anxiety. Furthermore, loneliness influences, either directly or through other mechanisms, biological markers of health, notably dysregulation of the neuroendocrine (hormone) system and systemic inflammation. These mechanisms are known risk factors for adverse health outcomes (Figure 1).

Figure 1. Possible mechanisms through which loneliness may influence morbidity and mortality.



Source: Adapted from Holt-Lunstad and Smith (2016).

Unhealthy lifestyle

Cross-sectional evidence shows that lonely individuals are more likely to engage in unhealthy behaviours. More precisely, compared to their non-lonely peers, lonely individuals are more likely to be smokers, abuse alcohol, be physically inactive and have a sedentary lifestyle (Åkerlind and Hörnquist, 1992; Lauder *et al.*, 2006; Hawkley, Thisted and Cacioppo, 2009; Shankar *et al.*, 2011). The evidence in longitudinal studies is limited but goes in the same direction. Hawkley et al. (2009) find that loneliness is associated with a lower likelihood of being physically active. Loneliness predicted a lower probability of finding employment in a study of 34 alcoholics treated in rehabilitation facilities (Hörnquist, Hansson and Åkerlind, 1988).

Two explanations have been put forward to rationalize why lonely individuals would adopt an unhealthier lifestyle. The first is the social control hypothesis: without loved ones around for support and control, individuals are less motivated to exercise, drink less alcohol, smoke less, etc. (Cacioppo, Capitanio and Cacioppo, 2014). The second hypothesis is based on self-regulation and executive function, which is the ability to make and implement plans, which are parts of cognitive function. As mentioned in the previous section, loneliness is associated with lower cognitive functioning, which, in turn, makes it harder to follow a healthier lifestyle (Hawkley, Thisted and Cacioppo, 2009; Cacioppo, Capitanio and Cacioppo, 2014).

Overall, there is evidence, although limited, that loneliness influences health through health-related behaviours. Unhealthy behaviour such as lack of exercise can in turn cause cardiovascular disease and, through the damage of blood vessels in the brain, dementia. However, many studies on the link between loneliness and health control for health-related behaviour, including the lifestyle factors discussed in this section, still find an association between loneliness and the health outcome. This implies that there are other relevant mechanisms for the link between loneliness and health besides health-related behaviour.

Sleep

Sleep problems are associated with adverse health outcomes like cardiovascular disease, weight gain, and diabetes, and sleeping badly increases mortality risk (National Academies of Sciences, Engineering, and Medicine, 2020). Loneliness appears to be linked to sleeping dysfunction (Choi, Irwin and Cho, 2015), including greater sleep fragmentation, worse sleep quality, and possibly greater daytime dysfunction but not sleep duration. Short-term studies show that lonely individuals display no differences in sleep duration but higher levels of sleep fragmentation, as measured with a device (Hawkley, Preacher and Cacioppo, 2010; Kurina *et al.*, 2011). The evidence on daytime dysfunction (*i.e.*, fatigue, low energy, sleepiness) is mixed, with higher levels of daytime dysfunction for a population-based sample from the USA (Hawkley, Preacher and Cacioppo, 2010), but no differences in daytime dysfunction among members of a traditional society in the USA (Kurina *et al.*, 2011).

Several other longitudinal studies find that feeling lonely is associated with lower subjective sleep quality (Jacobs *et al.*, 2006; McHugh and Lawlor, 2013), with sleep quality being an aggregate of seven components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction (McHugh and Lawlor, 2013). This link is partially explained by higher perceived stress among lonely individuals (McHugh and Lawlor, 2013).

An evolutionary hypothesis for the link between loneliness and sleep has been put forward by Hawkley et al. (2010). The authors suggest that being alone at night with nobody to keep watch would have been a potentially dangerous situation for our ancestors.

Feeling threatened and vulnerable would increase vigilance and lead to lighter, more fragmented, and thus less restful sleep.

Biological factors

Some of the biological health conditions associated with loneliness are themselves causes of other diseases. For instance, cardiovascular disease affects blood vessels in the brain and promotes the risk of cognitive decline and Alzheimer's disease (Rafnsson *et al.*, 2020). Loneliness may also affect health by changing the structure of the brain. Researchers rely on the idea of an individual's "cognitive reserve", which protects the brain structure and function against neuropathology and cognitive decline; it allows the recruitment of alternate mechanisms to pass information in the brain, compensating for cognitive difficulties related to damage to the brain (Shankar *et al.*, 2013; Kelly *et al.*, 2017). The cognitive reserve, and thus the additional brain infrastructure, is built up by cognitive stimulation, such as education and possibly communication and interaction with others, and would therefore be depleted by loneliness (Shankar *et al.*, 2013).

Finally, researchers observe a link between loneliness and biological indicators of health (biomarkers). This link may be direct or may pass through the health conditions associated with loneliness. These biomarkers concern the neuroendocrine (hormone) system and inflammation. More precisely, a higher level of the stress-related hormone cortisol is observed among lonely individuals compared to non-lonely individuals (Doane and Adam, 2010), and some markers of systematic inflammation are higher among lonely individuals (Nersesian *et al.*, 2018; Smith *et al.*, 2020). Among lonely women, markers of inflammation increased more in response to a lab-induced stressor than among non-lonely women (Hackett *et al.*, 2012). Higher levels of both stress hormones and inflammation can be described as the body's "defensive regime", which is prepared for threat and injury and increases the risk of cardiovascular diseases on the one hand and neural damage on the other hand, which then causes dementia (Rafnsson *et al.*, 2020).

Psychological factors

Among the psychological drivers of the relationship between loneliness and health, depression, anxiety, and stress represent the most prominent candidates. These factors

are significantly associated with loneliness and, in turn, may influence neuronal processes and biomarkers of health, leading to further adverse health outcomes (National Academies of Sciences, Engineering, and Medicine, 2020).

Stress is a recurrent theme in explaining the link between loneliness and health (Brown, Gallagher, and Creaven, 2018). It may explain part of the link between loneliness and cardiovascular disease (Christiansen, Larsen and Lasgaard, 2016), inflammation (Brown, Gallagher and Creaven, 2018), and sleep quality (McHugh and Lawlor, 2013). Moreover, levels of stress-related hormones are higher among lonely individuals (Doane and Adam, 2010). Furthermore, stress has been mentioned as a potential mechanism for the link between loneliness and cognitive decline (Rafnsson *et al.*, 2020).

The effect of stress may be twofold: (i) loneliness is a stressor itself, as a result of feeling chronic social threat as posited by the theoretical Loneliness Model (Cacioppo *et al.*, 2006, 2015); and (ii) loneliness makes it more difficult to deal with stress and then leads to a higher reactivity to stress. It has indeed been shown that relationships help individuals cope with stressors and, conversely, that loneliness is linked to a stronger physiological stress response (Hackett *et al.*, 2012; Brown, Gallagher and Creaven, 2018; National Academies of Sciences, Engineering, and Medicine, 2020). Stress, in turn, influences a wide range of health outcomes, some of which have been shown to be linked to loneliness: brain function, including cognitive function and memory; suppression of the immune system, cardiovascular disease; and gastrointestinal complications (Yaribeygi *et al.*, 2017).

To summarize, there are several potential mechanisms through which loneliness may influence health outcomes. Loneliness is correlated with an unhealthier lifestyle, worse sleep quality, and higher levels of stress, which are known health risk factors. Lonely individuals are less stimulated and thus have a smaller cognitive reserve to protect them against brain damage. Loneliness influences, either directly or through other mechanisms, biological markers of health, resulting notably in a dysregulation of the neuroendocrine system and systemic inflammation, which increase the risk of cardiovascular disease and brain damage. Furthermore, some of the health conditions associated with loneliness (see Section 2) can, in turn, cause other health problems. This includes depression, anxiety, and cardiovascular disease, which can in turn influence neuronal processes, biomarkers of health, and cognitive function. Finally, it is worth noting that the

mechanisms are highly interrelated. For example, loneliness is associated with stress, which is associated with cardiovascular disease, which can in turn affect dementia risk; or loneliness is associated with less physical activity, stress, and depression, which can influence sleep quality.

4. Reverse relation: health-related risk factors for loneliness

In the previous sections, we discussed how loneliness is related to different physical and mental health outcomes. However, we cannot exclude that some health conditions may have an independent effect on loneliness. These are generally conditions that make individuals less likely to be in contact and communicate with others, be it because of physical, cognitive, or psychological limitations. Inverse causality is a serious concern because it undermines the ability of traditional estimation techniques to isolate the direct and independent effect of loneliness on health. Casabianca and Kovacic (2022) show that, when the effects run in both directions, the estimated coefficient of loneliness is 3.5 times smaller in magnitude for depressive symptoms, 2.5 for suicidal intentions, and 6.4 times for functional decline.

Physical conditions associated with loneliness include functional decline or physical disability, hearing loss, as well as possibly poor physical health. Similarly, an increase in physical disabilities (*i.e.*, functional decline) is related to a higher risk of becoming lonely (Aartsen and Jylhä, 2011; Cohen-Mansfield *et al.*, 2016). In the study by Aartsen and Jylhä (2011), the association between physical disability and loneliness becomes insignificant when adjusting for other risk factors of loneliness, like loss of a partner and reduced social activity. A potential explanation is that physical disability influences loneliness through reduced social activity as a mechanism. A higher level of hearing impairment at the beginning of the study period is associated with lower levels of social functioning one year later, including “feeling lonely or remote”, “not feeling close to others” and “feeling left out even in a group” (Strawbridge *et al.*, 2000). On the other hand, the role of physical health in shaping loneliness is not clear. While Aartsen and Jylhä (2011) find that a decrease in self-perceived physical health was not significantly correlated with loneliness, the meta-analysis by Cohen-Mansfield et al. (2016) shows that poor physical health is a risk factor for loneliness.

Concerning cognitive limitations, Biddle et al., 2019 show that lower-range but normal cognitive performance is associated with a stronger decline in social engagement compared to higher-range cognitive performance, which may lead to increases in loneliness.

Finally, anxiety and depression may be associated with a higher risk of loneliness. According to the meta-analysis by Cohen-Mansfield et al. (2016), depression is a risk factor for loneliness, while another meta-analysis by Dahlberg et al. (2022) states that the role of depression is not clear-cut – some studies find that depression predicts future loneliness, while others find no effect. Domènech-Abella et al. (2019) show that anxiety is related to a higher risk of developing loneliness.

Overall, there is evidence that disability and hearing loss, depression and anxiety, as well as potentially cognitive impairment, are associated with a higher risk of becoming lonely. These health factors have in common that they make it more difficult to interact with others, either through reduced mobility, communication difficulties, reduced mental capacity, or in the case of depression, reduced energy. This suggests a mechanism for an effect of health on loneliness, where certain health conditions disrupt a person's social life and make it more difficult to maintain connections (Hawkley, 2020).

5. Conclusion

This review summarizes evidence on how loneliness may influence health and vice versa, as well as the potential underlying mechanisms.

There is robust evidence that loneliness is associated with increased mortality risk and is comparable to the mortality risk of obesity. However, it is not clear whether this is driven by loneliness itself or rather by social isolation. Loneliness is significantly associated with a higher risk of heart disease, high blood pressure, stroke, functional decline, and diabetes in terms of physical health, depression and suicide risk in terms of mental health; and finally, cognitive decline and dementia. There are also some studies showing that loneliness correlates with decreased immunity and anxiety.

Loneliness may be linked to health outcomes through several potential mechanisms, such as unhealthier lifestyle, worse sleep quality, and higher levels of stress, which are

known health risk factors. Loneliness influences, either directly or through other mechanisms, biological markers of health, resulting in a dysregulation of the neuroendocrine system and systemic inflammation, which increases the risk of cardiovascular disease and brain damage. Furthermore, some of the health conditions associated with loneliness can, in turn, cause other health problems. This includes depression, anxiety, and cardiovascular disease, which can in turn influence neuroendocrinal dysregulation and cognitive function.

The relationship between loneliness and health appears to run both ways. Not only is loneliness associated with a higher risk of certain health conditions, but some health conditions may also influence the likelihood of feeling lonely. This concerns conditions that make individuals less likely to connect and stay in touch with others, such as poor physical health, especially disability, hearing loss, depression, anxiety, and potentially cognitive impairment.

The reported evidence suggests that loneliness should be taken seriously as a risk factor for some severe health problems. Loneliness is comparable to other well-known risk factors for mortality, such as obesity, environmental quality, and physical activity. Similarly, loneliness as a risk factor for dementia is comparable to other factors like physical inactivity, low education, type 2 diabetes, and late-life depression.

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Annex – Summary of individual studies

Author (Year), Type	Topic, Topic fine grained	Data and Methodology	Outcome/Explanatory Variables	Results/Summary	Expected direction of effect (i.e. does loneliness have negative consequences as expected?)
Cacioppo et al. (2006), paper	- evolution: depression, anxiety	- cross-sectional - USA - hypnotic induction, F-test	- socioemotional variables: negative mood, positive mood, anger, anxiety, optimism, self-esteem, fear of negative evaluation, social skills, social support, intrusive thoughts avoidant thoughts - loneliness	An evolutionary theory of loneliness is outlined, and four studies replicate and extend prior research on the characteristics of lonely individuals. Studies 1 and 2 indicate that loneliness and depressed affect are related but separable constructs. Study 3 confirms that lonely, relative to nonlonely, young adults are higher in anxiety, anger, negative mood, and fear of negative evaluation, and lower in optimism, social skills, social support, positive mood, surgency, emotional stability, conscientiousness, agreeableness, shyness, and sociability. The set of six personality factors associated with loneliness (surgency, emotional stability, agreeableness, conscientiousness, shyness, and sociability) do not explain the associations between loneliness and negative mood, anxiety, anger, optimism (pessimism), self-esteem, and social support, as each association remained statistically significant even after statistically controlling for these personality factors. Study 4 used hypnosis to experimentally manipulate loneliness to determine whether there were associated changes in the participants' personality and socioemotional characteristics. Results confirmed that loneliness can influence the participants' personality ratings and socioemotional states. For study 4: Mean levels of loneliness after the hypnotic inductions were significantly different, F (1,19) = 109.56. individuals reported significantly greater negative mood, anxiety, and anger and significantly less optimism, self-esteem, and social support when induced to feel high compared to low loneliness	expected
Baarck et al. (2021), technical report	- general: COVID-19	- cross-sectional - EU countries - 2016-2020 - bivariate and multivariate analysis	- loneliness - country, demographic (age, gender), social (living arrangements, marital status), economic (income, education, employment status), and health-related characteristics	The COVID-19 pandemic has magnified already worrying levels of loneliness in Europe. Survey data shows that, in 2016, about 12% of EU citizens felt lonely more than half of the time. In the first months following the COVID-19 outbreak, this proportion doubled to around 25%.	expected
Hawkley et al. (2022) paper	- general: distribution of loneliness	- cross-sectional - USA - 2014, 2018 - non-parametric methods (locally weighted scatterplot smoothing), moderated regression models	- loneliness - age	We found a nonlinear relationship between age and loneliness that closely resembles prior research: age distribution of loneliness followed a nonlinear trajectory with elevated loneliness levels in oldest old (>70 years) and young adults (<30 years) with an additional peak at around 50–60 years. However, we found no evidence for age-specific predictors of loneliness. Household income, household size, marital status, health, and frequency of socializing were "universal" predictors of loneliness; their associations with loneliness did not differ in strength with age.	x
Lasgaard et al. (2016) paper	- general: distribution of loneliness	- cross-sectional - Denmark - 2013 - multinomial logistic regression	- loneliness - sociodemographic factors, health-related factors	The relation between loneliness and age took a shallow U-shaped distribution. Ethnic minority status, receiving disability pensions or being unemployed, living alone, prolonged mental disorder, and psychiatric treatment were strongly associated with severe loneliness. Socio-demographic and health-related factors were associated with an increased risk of severe loneliness in specific age groups. Being female, having a low educational level and living in a deprived area were only associated with loneliness in adolescence/emerging adulthood. Receiving	x

				disability pensions and living alone (i.e., divorced), on the other hand, were strongly associated with loneliness in early and middle adulthood and young-old age.	
Luhmann et al. (2016) paper	- general: distribution of loneliness	- cross-sectional - Germany - 2013 - non-parametric methods (locally weighted scatterplot smoothing), OLS	- loneliness - age	The age distribution of loneliness followed a complex nonlinear trajectory, with elevated loneliness levels among young adults and among the oldest old. The late-life increase in loneliness could be explained by lower income levels, higher prevalence of functional limitations, and higher proportion of singles in this age group. Consistent with an age-normative perspective, the association of income, relationship status, household size, and work status with loneliness differed between different age groups. In contrast, indicators of the quantity of social relationships (social engagement, number of friends, contact frequency) were universally associated with loneliness regardless of age.	x
Victor et al. (2012) paper	- general: distribution of loneliness	- cross-sectional - UK - 2006 - prevalence of loneliness conditioned on each of the risk factors, Gamma/chi-squared statistic	- loneliness - age	Loneliness demonstrates a nonlinear U-shaped distribution, with those aged under 25 years and those aged over 65 years demonstrating the highest levels of loneliness. Depression is associated with loneliness for all age groups. Poor physical health is associated with loneliness in young adult and midlife but not later life. For those in mid and later life, the quality of social engagement is protective against loneliness, while for young adults it is the quantity of social engagement. This indicates that different factors may endow vulnerability (or protect) against loneliness at different stages of life and suggests that preventative strategies or interventions that reflect these variations need to be developed.	x
Yang et al. (2011) paper	- general: distribution of loneliness	- cross-sectional - 25 European countries - 2006-2007 - multi-level models	- loneliness - age, country of residence	The prevalence of loneliness increases with age for the combined sample. However, the nation in which one lives shows a greater impact than age on reported levels of loneliness, with Russia and Eastern European nations having the highest proportions of lonely people (about 10–34% for different age groups) and Northern European nations the lowest (mostly below 6%).	x
Dahlberg et al. (2018) paper	- general: trend of loneliness	- cross-sectional - Sweden - 1992/2004-2014 - linear and logistic regression analyses	- loneliness - gender, age in years and educational level, marital status, social support and social contacts, limitations in activities of daily living (ADL), psychological distress	Contrary to what is often assumed, there has been no increase in loneliness among older people over time (1992–2014). Regression analyses for 2004 and 2014 showed that social and health-related correlates were more strongly associated with loneliness than socio-demographic correlates. Psychological distress was most strongly associated with loneliness, followed by widowhood. Most associations between the correlates and loneliness were stable over time.	opposite
Hörnquist et al. (1988) paper	- mechanisms: alcohol abuse	- longitudinal, 2 years - Sweden - 1979/1980-1981/1982 - stepwise multiple regression analyses	- rehabilitation from alcohol abuse - loneliness	Those who felt less lonely and had no drinking buddies appeared most likely to be rehabilitated vocationally.	expected
Lauder et al. (2006) paper	- mechanisms: health behaviour	- cross-sectional - Australia - 2003 - chi2-test, Mann – Whitney U-Test, logistic regression, ANCOVA	- health behaviours (smoking, overweight, BMI, sedentary, attitudes towards physical activity) - loneliness	Lonely individuals were more likely to be smokers and more likely to be overweight – obese. The lonely group had higher body mass index scores controlling for age, annual income, gender, employment and marital status. Logistic regression revealed no differences in sedentary lifestyles. Lonely individuals were significantly less likely to believe it was desirable for them to lose weight by walking for recreation, leisure or transportation.	expected
Shankar et al. (2011) paper	- mechanisms: health behaviour	- cross-sectional - UK - 2004;	- health behaviours: smoking and physical, biological factors: blood pressure, cholesterol, and inflammatory	Both social isolation and loneliness were associated with a greater risk of being inactive, smoking, as well as reporting multiple health-risk behaviours. Social isolation was also positively associated with blood pressure, C-reactive protein, and fibrinogen levels. Loneliness and social isolation may affect	expected

			markers - loneliness, social isolation	health independently through their effects on health behaviours. In addition, social isolation may also affect health through biological processes associated with the development of cardiovascular disease.	
Christiansen et al. (2016) paper	- mechanisms: health behaviour, sleep	- cross-sectional - Denmark - 2013 - mediation analyses	- loneliness - Cardiovascular disease, diabetes, and migraine	Findings show that loneliness was significantly associated with cardiovascular disease, diabetes, and migraine. In addition high perceived stress, physical inactivity, daily smoking, and poor sleep mediated the association between loneliness and adverse health conditions.	expected
Nersesian et al. (2018) paper	- mechanisms: inflammation	- cross-sectional, 3 days - USA - 2004-2009 - hierarchical regression	- systematic inflammation (Three pro-inflammatory cytokines—IL-6, fibrinogen, and CRP) - loneliness	There was a positive significant relationship between loneliness and the three systemic inflammation biomarkers after controlling for covariates: interleukin-6 (n=873) (b[se]=0.07[0.03], p=.014); fibrinogen (n=867) (b[se]= 18.24[7.12], p=.011); and C-reactive protein (n=867) (b[se]= 0.08[0.04], p=.035). Feeling lonely was strongly positively correlated with self-reports of more stress.	expected
Hackett et al. (2012) paper	- mechanisms: inflammation, neuroendocrine disruption	- cross-sectional - UK - 2006-2008 - OLS, logistic regression	- inflammation biomarkers - loneliness, stress	The aim of the study was to investigate the relationship between loneliness and inflammatory interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra) and monocyte chemotactic protein-1 (MCP-1) responses to standardized mental stress. A secondary purpose was to evaluate whether individual variations in cortisol responses influenced the hypothesised relationship between loneliness and inflammation. Greater loneliness was associated with larger IL-6 ($p = 0.044$) and IL-1Ra ($p = 0.006$) responses to psychological stress and higher MCP-1 ($p < 0.001$) levels in women, independently of age, grade of employment, body mass index and smoking status. No associations were observed in men. Cortisol responsivity was inversely related to loneliness in women, with the odds of being a cortisol responder decreasing with increased loneliness independently of covariates ($p = 0.008$).	inconclusive for men, expected for women
Hawkley et al. (2009) paper	- mechanisms: physical activity	- longitudinal, 3 years - USA - 2002/2003 - cross-sectional: Binary logistic regression analysis, longitudinal: latent variable growth models	- changes in physical activity probability over a 3-year period - loneliness	Longitudinal analyses revealed that loneliness predicted diminished odds of physical activity in the next two years (OR = 0.61), and greater likelihood of transitioning from physical activity to inactivity (OR = 1.58)	expected
Hawkley et al. (2010) paper	- mechanisms: sleep	- cross-sectional, 3 days - USA - 2002/2003 - cross-lagged panel models	- sleep duration, daytime dysfunction (i.e., fatigue, low energy, sleepiness) - loneliness	Daily variations in loneliness predicted subsequent feelings of daytime dysfunction ($B = 0.16$, $p < .05$), and daytime dysfunction predicted subsequent loneliness ($B = 0.07$, $p < .05$), adjusted for covariates. Loneliness continued to predict subsequent daytime dysfunction when depressed affect was held constant. The effect of loneliness on daytime dysfunction was independent of sleep duration, suggesting that the same amount of sleep is less salubrious when individuals feel more socially isolated. Sleep duration was not associated with loneliness, or daytime dysfunction.	expected
Jacobs et al. (2006) paper	- mechanisms: sleep	- longitudinal, 7 years - Israel - 1990-1998 - logistic regression analysis	- global sleep satisfaction (GSS) - loneliness	In a regression analysis, risk factors at age 70 for subsequent poor global sleep satisfaction (GSS) were loneliness, depression, poor self-rated health, economic difficulties, back pain, obesity, and prior poor GSS.	expected
Kurina et al. (2011) paper	- mechanisms: sleep	- cross-sectional, 7 days - USA - cross-sectional analysis: logistic	- sleep fragmentation, sleep duration, subjective sleep quality, subjective daytime sleepiness - loneliness	Higher loneliness scores were associated with significantly higher levels of sleep fragmentation (ß = 0.073, t = 2.55, P = 0.01), controlling for age, sex, body mass index, risk of sleep, apnea, and negative affect (a factor comprising symptoms of depression and anxiety, and perceived stress). Loneliness was not associated with sleep duration or with either subjective	inconclusive for subjective sleep quality, expected for sleep fragmentation

		regression, longitudinal analysis: latent variable growth models		sleep measure.	
McHugh et al. (2013) paper	- mechanisms: sleep	- longitudinal, 2 years - 2007/2009 + 2 years - multivariate regression analysis	- sleep quality - loneliness, stress	We found that loneliness, specifically emotional loneliness, predicted sleep quality at follow-up, controlling for demographic factors and for sleep quality at baseline. Upon applying mediation methods to the data, we then found that this relationship was mediated in part by perceived stress. We conclude that the impact of emotional loneliness on sleep quality in older adults is partly because of the stress experienced as a result of feeling lonely.	expected
Doane et al. (2010) paper	- mechanisms: stress	- cross-sectional - USA - three-level hierarchical growth curve models	- cortisol levels - loneliness	In a community sample of young adults, multilevel modelling was used to examine whether trait and state feelings of loneliness were related to changes in levels of the stress-sensitive hormone cortisol. Results indicated that trait loneliness was associated with a flattening of the diurnal cortisol rhythm. In addition, both daily and momentary state variations in loneliness were related to cortisol. Prior day feelings of loneliness were associated with an increased cortisol awakening response the next morning and momentary experiences of loneliness during the day were associated with momentary increases in cortisol among youth who also had high chronic interpersonal stress. Results were significant after covarying current depression, both chronic and momentary reports of stress, and medical and lifestyle covariates.	expected
Domènech-Abella et al. (2019) paper	- morbidity: anxiety, depression	- longitudinal, 2 years - Ireland - 2021/13-2014/15 - logistic regression	- generalized anxiety disorder (GAD) and major depression disorder (MDD) - loneliness, social networks	The longitudinal association between experiencing loneliness and higher likelihood of suffering from generalized anxiety disorder (GAD) two years later is bidirectional, whereas the association between social isolation and higher likelihood of subsequent major depression disorder (MDD) or GAD as well as those between loneliness and subsequent MDD or deterioration of social integration are unidirectional	expected
Hawkley et al. (2010) paper	- morbidity: blood pressure	- longitudinal, 5 years - USA - 2002/2003-2006 - Cross-lagged panel analyses	- systolic blood pressure (SBP) - loneliness	loneliness at study onset predicted increases in systolic blood pressure (SBP) 2, 3, and 4 years later (B 0.152, SE 0.091, p .05, one-tailed). These increases were cumulative such that higher initial levels of loneliness were associated with greater increases in SBP over a 4-year period	expected
Caspi et al. (2006) paper	- morbidity: cardiovascular disease	- longitudinal - New Zealand, Dunedin - 1972/73-1998/99 - OLS, Risk ratios with controls	- cardiovascular multifactorial risk status (overweight, elevated blood pressure, elevated total cholesterol level, low high-density lipoprotein level, elevated glycated haemoglobin concentration, and low maximum oxygen consumption) - social isolation	Socially isolated children were at significant risk of poor adult health (adult cardiovascular multifactorial risk status) compared with non-isolated children (risk ratio, 1.37; 95% confidence interval, 1.17- 1.61). This association was independent of other well-established childhood risk factors for poor adult health (low childhood socioeconomic status, low childhood IQ, childhood overweight), was not accounted for by health damaging behaviours (lack of exercise, smoking, alcohol misuse), and was not attributable to greater exposure to stressful life events. In addition, longitudinal findings showed that chronic social isolation across multiple developmental periods had a cumulative, dose-response relationship to poor adult health (risk ratio, 2.58; 95% confidence interval, 1.46-4.56)	expected
Valtorta et al. (2018) paper	- morbidity: cardiovascular disease	- longitudinal, avg. 5.4 years - UK - 2004-2010 - odds ratio	- coronary heart disease, stroke - loneliness, social isolation	We found that loneliness was associated with an increased risk of cardiovascular disease (odds ratio 1.27, 95% confidence interval 1.01–1.57). Social isolation, meanwhile, was not associated with disease incidence. Loneliness is associated with an increased risk of developing coronary heart disease and stroke, independently of traditional cardiovascular disease risk factors. There was no evidence of a cumulative effect over time of social relationships on cardiovascular disease risk.	expected
Holwerda et al. (2014)	- morbidity:	- longitudinal, 3 years	- dementia - loneliness	After adjustment for other risk factors, older persons with feelings of loneliness were more likely to develop dementia (OR	expected

paper	cognitive decline/dementia	- Netherlands - 1990/1991-1993/1994 - logistic regression		1.64, 95% CI 1.05 to 2.56) than people without such feelings. Social isolation was not associated with a higher dementia risk in multivariate analysis.	
Rafnsson et al. (2020) paper	- morbidity: cognitive decline/dementia	- longitudinal - UK - 2004-2012 - Cox proportional hazards regression models	- dementia - loneliness, (number of close relationships, marital status, social isolation)	Dementia risk was positively related to greater loneliness (hazard ratio 1.40, 95% confidence interval 1.09–1.80, p = .008), and inversely associated with number of close relationships (p < .001) and being married (p = .018). Sensitivity analyses testing for reverse causality and different criteria for diagnosing dementia confirmed the robustness of these findings. There was no association with social isolation. However, greater loneliness was associated with future dementia risk (Model 3, adjusted HR 1.44, 95% CI 1.11–1.88, p = .006). There was a 44% increase in the risk of future dementia for every unit change in loneliness rating independent of covariates. Model 5 introduced all the social relationship variables simultaneously, along with covariates. Marriage, loneliness, and number of close relationships remained independent predictors of dementia, with a small reduction in the strength of the association for loneliness (hazards ratio change from 1.44 to 1.33).	expected
Shankar et al. (2013) paper	- morbidity: cognitive decline/dementia	- longitudinal, 4 years - UK - 2004-2008 - regression analysis	- cognitive function (verbal fluency/executive function, immediate recall, and delayed recall) - loneliness, social isolation	Loneliness was associated with poorer immediate recall (ß = -.05, p < .001) and delayed recall (ß = -.03, p = .02)	expected
Wilson et al. (2007) paper	- morbidity: cognitive decline/dementia	- longitudinal, 4 years - USA - 2000-2006 - Alzheimer's disease risk: Cox proportional hazard models, Cognitive decline: mixed-effects models	- Alzheimer's disease, dementia, global cognition and specific cognitive functions (episodic memory, semantic memory, working memory, perceptual speed, visuospatial ability), pathological assessment of the brain (cerebral infarctions) - loneliness	Risk of Alzheimer's disease (AD) was more than doubled in lonely persons (score 3.2, 90th percentile) compared with persons who were not lonely (score 1.4, 10th percentile), and controlling for indicators of social isolation did not affect the finding. Loneliness was associated with lower level of cognition at baseline and with more rapid cognitive decline during follow-up. There was no significant change in loneliness, and mean degree of loneliness during the study was robustly associated with cognitive decline and development of AD. In 90 participants who died and in whom autopsy of the brain was performed, loneliness was unrelated to summary measures of AD pathology or to cerebral infarction.	inconclusive for cerebral infarction during autopsy, expected for cognitive function
Jeuring et al. (2018) paper	- morbidity: depression	- longitudinal, 6 years - Netherlands - 2007/2010 + 6 years - multinomial regressions, mixed model analyses	- six-year prognosis of patients with late-life depression (symptom severity and depression diagnosis) and to identify prognostic factors of an unfavourable course - loneliness (and other factors)	Among depressed patients at baseline, 46.8% were lost to follow-up; 15.9% had an unfavourable course, i.e., chronic or recurrent; 24.6% had partial remission; and 12.7% had full remission at six-year follow-up. The relative risk of mortality in depressed patients was 2.5 (95% confidence interval 1.26–4.81) versus non-depressed comparisons. An unfavourable course of depression was associated with a younger age at depression onset; higher symptom severity of depression, pain, and neuroticism; and loneliness at baseline. Additionally, partial remission was associated with chronic diseases and loneliness at baseline when compared with full remission.	expected
Lukaschek et al. (2017) paper	- morbidity: diabetes	- longitudinal, avg. 14.0 years - Germany - 1989-2009 - Cox regression	- type 2 diabetes - social network satisfaction (SNS)	In men with low social network satisfaction (SNS), risk for incident type 2 diabetes (T2D) increased significantly (HR: 2.15, 95% CI: 1.33–3.48, p value 0.002). After additional adjustments for social isolation or living alone, the risk for incident T2D was still significant, albeit less pronounced (HRs 1.85 or 2.05, p values 0.001 or 0.004).	expected
Buchman et al. (2010) paper	- morbidity: functional decline	- longitudinal, up to 12 years (annual) - USA - Linear mixed-effects models,	- global motor functioning, consisting of 9 measures of muscle strength and 9 motor performances - loneliness	Linear mixed-effects models which controlled for age, sex and education, showed that the level of loneliness at baseline was associated with the rate of motor decline (Estimate, -0.016; S.E. 0.006, p = 0.005). For each 1-point higher level of loneliness at baseline, motor decline was 40% more rapid; this effect was similar to the rate of motor decline observed in an average participant 4 years older at baseline. Furthermore, this amount	expected

		Cox proportional hazards		of motor decline per year was associated with about a 50% increased risk of death. When terms for both feeling alone (loneliness) and being alone were considered together in a single model, both were relatively independent predictors of motor decline. The association between loneliness and motor decline persisted even after controlling for depressive symptoms, cognition, physical and cognitive activities, chronic conditions, as well as baseline disability or a history of stroke or Parkinson's disease.	
Casabianca et al. (2022) paper	- morbidity: general	- causal (instrumental variables) - 28 European countries + Israel - 2015-2021 - two-stage least squares (IV)	- depressive symptoms, number of limitations with activities of daily living (ADL); body mass index (BMI); number of chronic diseases, self-assessed health, consumption of drugs (medicines) for six health problems, namely anxiety, sleeping problems, cholesterol	The results suggest that loneliness directly increases the probability of depression (Eurod), functional decline (Adl), and high body mass index (Bmi). More specially, a gradual increase in loneliness causes a 1.81 point increase in the intensity of depressive symptoms as measured by the EURO-D scale (ranging from 0 to 12), 0.45 more limitations in daily activities, and a 4.5 point increase in the body mass index. Finally, loneliness does not significantly influence the incidence of chronic conditions or the perception of general health. When considering physical health-related factors separately we see that loneliness increases the probability of diabetes by 6% and high blood pressure by 12%. In addition to health outcomes, loneliness significantly affects the prevalence of drug use for sleeping problems, anxiety, pain, and high blood pressure. Being lonely increases the probability of medication for high blood pressure by 14%, for anxiety by 3.3%, for pain by 8.4% and for sleeping problems by 4.5%.	expected
Richard et al. (2017) paper	- morbidity: general	- cross-sectional - Switzerland - 2012 - logistic regression (OR)	- physical and mental health or lifestyle characteristics - loneliness	Lonely individuals were more often affected by physical and mental health problems, such as self-reported chronic diseases (Odds ratio [OR] 1.41, 95% confidence interval [CI] 1.30–1.54), high cholesterol levels (OR 1.31, 95% CI 1.18–1.45), diabetes (OR 1.40, 95% CI 1.16–1.67), moderate and high psychological distress (OR 3.74, 95% CI 3.37–4.16), depression (OR 2.78, 95% CI 2.22–3.48) and impaired self-perceived health (OR 1.94, 95% CI 1.74–2.16). Loneliness was significantly associated with most lifestyle factors (e.g. smoking; OR 1.13, 95% 1.05–1.23).	expected
LeRoy et al. (2017) paper	- morbidity: immunity	- assessment during 5 days after artificial infection with the common cold - USA - OLS, hierarchical multiple regression	- subjective and objective cold symptoms - loneliness, social isolation	After adjusting for demographics, season of participation, depressive affect, and social isolation, a logistic regression revealed that participants who were lonely were no more likely to get infected with the virus than less lonely participants (OR=0.994, p=.941). loneliness predicted self-reported cold symptoms over time. social network size and diversity did not predict cold symptoms. These findings suggest that the perception of loneliness is more closely linked to self-reported illness symptoms than objectively measured social isolation. Lastly, we ran an ancillary analysis to examine whether loneliness was also associated with an objective common cold indicator (i.e., mucus weight). When we replaced self-reported symptoms with mucus weight for each model (Aims 1–3), none were significant (all p values > .56).	inconclusive for infection, expected for self-reported symptoms
Pressman et al. (2005) paper	- morbidity: immunity	- longitudinal, 4 months - USA - 2001/2002 - multiple linear regressions	- postimmunization Ab levels, health behaviours, and cortisol levels - loneliness	Antibody response to the influenza immunization was investigated in 83 1st-semester healthy university freshmen. Elevated levels of loneliness throughout the semester and small social networks were independently associated with poorer antibody response to 1 component of the vaccine. Those with both high levels of loneliness and a small social network had the lowest antibody response.	expected
Beutel et al. (2017) paper	- morbidity: mental health	- cross-sectional (pools the panel) - Germany - 2007-2012 - logistic regression (OR)	- depression, generalized anxiety, and suicidal ideation - loneliness	A total of 10.5% of participants reported some degree of loneliness (4.9% slight, 3.9% moderate and 1.7% severely distressed by loneliness). Loneliness declined across age groups. Loneliness was stronger in women, in participants without a partner, and in those living alone and without children. Controlling for demographic variables and other sources of distress loneliness was associated with depression (OR = 1.91), generalized anxiety (OR = 1.21) and suicidal ideation (OR = 1.35).	expected

				Lonely participants also smoked more and visited physicians more frequently.	
Cacioppo et al. (2010) paper	- morbidity: mental health	- longitudinal, 5 years - USA - 2002-2006 - autoregressive cross-lagged panel models, test for reciprocal predictive relationships	- loneliness and depressive symptoms, considered simultaneously - loneliness and depressive symptoms, considered simultaneously	Cross-lagged analyses indicated that loneliness predicted subsequent changes in depressive symptomatology, but not vice versa, and that this temporal association was not attributable to demographic variables, objective social isolation, dispositional negativity, stress, or social support.	expected
Bennardi et al. (2019) paper	- morbidity: suicidality	- longitudinal, average 3.5 years - Spain - 2011/12-2014/15 - logistic regression	- suicide ideation, suicide planning, and attempts - loneliness	Feelings of loneliness were related to suicidal ideation in 60-year-and-older individuals, but not for those 18-59 years old.	inconclusive for younger individuals, expected for older individuals
Van Orden et al. (2015) paper	- morbidity: suicidality	- interview, longitudinal, 1 year - Sweden - 2003-2006 - interview + follow-up	- suicide attempt - loneliness	We investigated older adults' causal attributions for suicidal behaviour. Attributions included: a desire to escape (n=29), reduced functioning and autonomy (n=24), psychological problems, including depression (n=24), somatic problems and physical pain (n=16), perceived burdensomeness (n=13), social problems that reflected either thwarted belongingness or family conflict (n=13) and lack of meaning in life (n=8). As hypothesized, patients who attributed the attempt to thwarted belongingness were more likely to use more immediately lethal means for their index attempt and were more likely to re-attempt during follow-up.	expected
Van Wijngaarden et al. (2015) paper	- morbidity: suicidality	- interview (qualitative) - Netherlands - 2013 - reflective lifeworld research design	- suicide ideation - loneliness	The aim of this paper is to describe the phenomenon 'life is completed and no longer worth living' from a lifeworld perspective, as it is lived and experienced by elderly people. The essential meaning of the phenomenon is understood as 'a tangle of inability and unwillingness to connect to one's actual life', characterized by a permanently lived tension: daily experiences seem incompatible with people's expectations of life and their idea of whom they are. While feeling more and more disconnected to life, a yearning desire to end life is strengthened. The experience is further explicated in its five constituents: 1) a sense of aching loneliness; 2) the pain of not mattering; 3) the inability to express oneself; 4) multidimensional tiredness; and 5) a sense of aversion towards feared dependence.	expected
Wiktorsson et al. (2010) paper	- morbidity: suicidality	- cross-sectional - Sweden - 2003-2006 - chi2-test, t-test	- suicide attempt - loneliness	Factors associated with attempted suicide included being unmarried, living alone, low education level, history of psychiatric treatment, and previous suicide attempt. There was no association with dementia. An association was observed between perceived loneliness and attempted suicide; this relationship was independent of depression (OR: 2.8, 95% CI: 1.3–6.1).	expected
Beller et al. (2018) paper	- mortality	- longitudinal, 20 years - Germany - 1996-2016 - bivariate and multiple Cox survival regression analyses	- mortality - loneliness, social isolation	We found that the effects of loneliness and social isolation synergistically interact with each other: The higher the social isolation, the larger the effect of loneliness on mortality, and the higher the loneliness, the larger the effect of social isolation. Conclusions: Both constructs are important in predicting health. Regarding the bivariate Cox survival regression, both loneliness and social isolation significantly predicted an increased mortality with HRs of 1.24 and 2.85, respectively, p-values < .001.	expected
Elovainio et al. (2017) paper	- mortality	- longitudinal, 6.5 years - UK - 2007-2010, +	- all-cause and cause-specific mortality - loneliness, social isolation	The hazard ratio for all-cause mortality for social isolation compared with no social isolation was 1.73 (95% CI 1.65–1.82) after adjustment for age, sex, ethnic origin, and chronic disease (i.e.	inconclusive

		follow-up - Cox proportional hazards models		minimally adjusted), and was 1.26 (95% CI 1.20–1.33) after further adjustment for socioeconomic factors, health-related behaviours, depressive symptoms, biological factors, cognitive performance, and self-rated health (i.e. fully adjusted). The minimally adjusted hazard ratio for mortality risk related to loneliness was 1.38 (95% CI 1.30–1.47), which reduced to 0.99 (95% CI 0.93–1.06) after full adjustment for baseline risks.	
Shiovitz-Ezra et al. (2010) paper	- mortality	- NA - USA - 1996-2000 + mortality data up to 2004 - Cox proportional hazard model	- mortality - loneliness	Those identified as "situationally lonely" (HR = 1.56; 95% CI: 1.52–1.62) as well as those identified as "chronically lonely" (HR = 1.83; 95% CI: 1.71–1.87) had a greater risk for all-cause mortality net of the effect of possible demographic and health confounders. Nonetheless, relative to those classified as "situationally lonely," individuals classified as "chronically lonely" had a slightly greater mortality risk.	expected
Steptoe et al. (2013) paper	- mortality	- longitudinal (7.25 years of follow up on average) - UK - 2004-2012 - Cox proportional hazards models	- all-cause mortality - loneliness, social isolation	We found that mortality was higher among more socially isolated and more lonely participants. However, after adjusting statistically for demographic factors and baseline health, social isolation remained significantly associated with mortality (hazard ratio 1.26, 95% confidence interval, 1.08– 1.48 for the top quintile of isolation), but loneliness did not (hazard ratio 0.92, 95% confidence interval, 0.78–1.09). Social isolation and loneliness were positively correlated (<U+03C1> = 0.10, P < 0.001).	inconclusive
Tanskanen et al. (2016) paper	- mortality	- longitudinal, 17 years - Finland - 1994-2011 - Cox regression using general additive models	- mortality - loneliness and social isolation	Social isolation and loneliness, when examined separately, were connected to an elevated all-cause mortality risk. When isolation and loneliness were estimated simultaneously, the effect of loneliness became insignificant, whereas that of social isolation maintained a significant mortality risk (HR = 1.009; 95% CI = 1.006, 1.013).	inconclusive
Hakulinen et al. (2018) paper	- mortality, morbidity: cardiovascular disease	- longitudinal, avg. 7.1 years - UK - 2007-2010, + follow-up - Cox proportional hazards models	- acute myocardial infarction (AMI), stroke, mortality - loneliness, social isolation	For AMI and stroke, loneliness and social isolation are both relevant, when adjusting for age, sex, ethnicity: When loneliness, social isolation and the interaction between social isolation and loneliness were entered in the same model, social isolation and loneliness were associated with higher risk of AMI (social isolation: HR 1.36, 95% CI 1.25 to 1.49, P<0.001; loneliness: HR 1.42, 95% CI 1.27 to 1.59, P<0.001) and incident stroke (social isolation: HR 1.37, 95% CI 1.22 to 1.54, P<0.001; loneliness: HR 1.35, 95% CI 1.17 to 1.56, P<0.001) in the analyses additionally adjusted for sex, age and ethnicity. The interaction terms between social isolation and loneliness were not statistically significant (all P >0.05).	inconclusive
Luo et al. (2012) paper	- mortality, morbidity: depression, functional decline	- longitudinal - USA - 2002-2008 - cross-lagged panel models	- loneliness, mortality, depressive symptoms, self-rated health, functional limitations - x	Feelings of loneliness were associated with increased mortality risk over a 6-year period, and that this effect was not explained by social relationships or health behaviours but was modestly explained by health outcomes. In cross-lagged panel models that tested the reciprocal prospective effects of loneliness and health, loneliness both affected and was affected by depressive symptoms and functional limitations over time, and had marginal effects on later self-rated health.	expected
Perissinotto et al. (2012) paper	- mortality, morbidity: functional decline	- longitudinal, 6 years - USA - 2002-2008 - death risk: proportional hazards model, functional decline: modified Poisson regression analyses	- mortality, functional decline - loneliness	Among participants who were older than 60 years, loneliness was a predictor of functional decline and death. Lonely subjects were more likely to experience decline in activities of daily living (ADL) (24.8% vs 12.5%; adjusted risk ratio [RR], 1.59; 95% CI, 1.23-2.07). Develop difficulties with upper extremity tasks (41.5% vs 28.3%; adjusted RR, 1.28; 95% CI, 1.08- 1.52); experience decline in mobility (38.1% vs 29.4%; adjusted RR, 1.18; 95% CI, 0.99-1.41); or experience difficulty in climbing (40.8% vs 27.9%; adjusted RR, 1.31; 95% CI, 1.10-1.57). Loneliness was associated with an increased risk of death (22.8% vs 14.2%; adjusted HR, 1.45; 95% CI, 1.11-1.88).	expected
Biddle et al. (2019)	- reverse con-	- longitudinal, 3 years	- social engagement - baseline cognitive	Lower baseline Preclinical Alzheimer Cognitive Composite (PACC) score was associated with decline in social engagement	expected

paper	nection: cognitive decline/dementia	- USA - multivariable regression models	performance, amyloid-beta	score (b = 1.1, p = 0.02)	
Aartsen et al. (2011) paper	- reverse connection: general	- longitudinal, up to 28 years - Finland - 1979-2006 - bivariate and multivariate logistic regression analysis	- loneliness - increased physical disability	Logistic regression analyses indicated that losing a partner, reduced social activities, increased physical disabilities, increased feelings of low mood, uselessness and nervousness, rather than baseline characteristics, are related to enhanced feelings of loneliness at follow-up. The higher incidence of loneliness among women can be fully explained by the unequal distribution of risk factors among men and women (e.g., women more often become widowed).	expected
Strawbridge et al. (2000) paper	- reverse connection: hearing loss	- longitudinal, 1 year - USA - 1994/1995 - logistic regression models	- social functioning (including loneliness) - hearing impairment	Having a hearing impairment is related to higher levels of loneliness one year later. Loneliness increases in a dose-response pattern for those with progressive levels of hearing impairment compared with those reporting no impairment.	expected
Hawkley (2020) viewpoint	- general			Social integration was once thought to have effects on health via health behaviours, but we now know that the effects of perceived social isolation include biological consequences, therefore implicating direct central nervous system control. Loneliness is itself a product of central processes, including implicit hypervigilance for social threat, diminished self-regulatory capacity, and maladaptive social cognitions that bias lonely relative to socially connected individuals to perceive, expect, and remember more negative social information. Interventions that address maladaptive social cognitions have been shown to be more successful in reducing felt loneliness than interventions that work to increase number of social contacts.	opposite
Hawkley et al. (2010) review	- general			Chronic perceived isolation (i.e., loneliness) is characterized by impairments in attention, cognition, affect, and behaviour that take a toll on morbidity (including cardiovascular health risk, depression, suicide, cognitive decline, dementia) and mortality through their impact on genetic, neural, and hormonal mechanisms that evolved as part and parcel of what it means to be human.	expected
Leigh-Hunt et al. (2017) review of reviews	- general			Meta-analyses have identified a significant association between social isolation and loneliness with increased all-cause mortality and social isolation with cardiovascular disease. Narrative systematic reviews suggest associations with poorer mental health outcomes, with less strong evidence for behavioural and other physical health outcomes. No reviews were identified for wider socio-economic or developmental outcomes.	expected
National Academies of Sciences et al. (2020) review (book)	- general			Comprehensive review of the impacts of social isolation and loneliness on mortality and morbidity, the risk factors, the mechanisms by which social isolation and loneliness impact health, the factors that affect those mechanisms, and the ways in which researchers measure social isolation and loneliness and their resultant impacts on health. Social isolation and loneliness are strongly associated with a greater incidence of major psychological, cognitive, and physical morbidities and lower perceived well-being or quality of life. This includes cardiovascular and cerebrovascular morbidities, chronic health conditions, such as type 2 diabetes mellitus, or on health characteristics, such as mobility and functioning in the activities of daily living, accelerated cognitive decline in older adults and an increased risk of incident dementia, depression and anxiety. Risk and protective factors for social isolation and loneliness include predisposing physical health factors (e.g., chronic diseases like heart disease, stroke, and cancer, functional impairments, sensory impairments (hearing loss)); psychological,	expected

				psychiatric, and cognitive factors (e.g., depression, anxiety, dementia); socio-cultural factors (e.g., social supports, disruptive life events); and social environmental factors (e.g., transportation, housing). Strong evidence links loneliness, social isolation, and social support to changes in cardiovascular, neuroendocrine, and immune function as well as to the physiological stress response. A lack of social connections has been linked to higher levels of inflammation, which may point to a plausible biological mechanism for the association of social isolation and loneliness with a variety of negative health outcomes. Social isolation and loneliness have been linked to decreased quality of sleep, which itself can influence a variety of physical health conditions, including cardiovascular disease, weight gain and obesity, diabetes, metabolic syndrome, and increased risk for mortality.	
Ong et al. (2016) review	- general			Independent of objective features of social relationships loneliness has been associated with impaired daytime functioning, reduced physical activity, lower subjective well-being, and poorer physical health. Moreover, beyond cross-sectional associations, loneliness has been shown to prospectively predict increased depressive symptomatology, impaired cognitive performance, dementia progression, significant likelihood of nursing home admission, and multiple disease outcomes (e.g., hypertension, heart disease, and stroke in older persons)	expected
Perlman et al. (1984) book	- general			x	
Åkerlind et al. (1992) review	- mechanisms: alcoholism			Knowledge is still incomplete, but the review indicates that loneliness may be significant at all stages in the course of alcoholism as a contributing and maintaining factor in the growth of abuse and as an encumbrance in attempts to give it up. Concordant reports demonstrate that alcoholics do feel more lonely than members of most other groups do. In advanced abusers, loneliness is obviously connected with a number of negative characteristics and, together with several of those, directly linked to a poor prognosis.	expected
Holt-Lunstad et al. (2016) viewpoint	- mechanisms: cardiovascular disease			There is substantial research indicating broad health risks (e.g., immune functioning, cardiovascular functioning, cognitive decline) associated with the quantity and quality of social relationships—including several meta-analyses documenting mortality risk.	expected
Smith et al. (2020) review	- mechanisms: inflammation			The review synthesised evidence examining the association between a. loneliness with inflammation and b. social isolation with inflammation. There was no association between loneliness with CRP or fibrinogen, but there was a significant association between loneliness and IL-6 for most-adjusted but not least-adjusted analyses. Results indicate that social isolation and loneliness could be linked with systemic inflammation, but more robust methodology is needed to confirm these associations and unpack mechanisms.	inconclusive/expected
Brown et al. (2018) review	- mechanisms: stress reactivity			Overall, the majority of studies reported positive associations between loneliness and acute stress responses, such that higher levels of loneliness were predictive of exaggerated physiological reactions. However, in a few studies, loneliness was also linked with decreased stress responses for particular physiological outcomes, indicating the possible existence of blunted relationships. There was no clear pattern suggesting any sex- or stressor-based differences in these associations. The available evidence supports a link between loneliness and atypical physiological reactivity to acute stress. A key finding of this review was that greater levels of loneliness are associated with exaggerated blood pressure and inflammatory reactivity to acute stress. However, there was some indication that lone-	inconclusive/expected

				liness may also be related to blunted cardiac, cortisol, and immune responses. Overall, this suggests that stress reactivity could be one of the biological mechanisms through which loneliness impacts upon health.	
Valtorta et al. (2016) meta-analysis	- morbidity: cardiovascular disease			Poor social relationships were associated with a 29% increase in risk of incident CHD (pooled relative risk: 1.29, 95% CI 1.04 to 1.59) and a 32% increase in risk of stroke (pooled relative risk: 1.32, 95% CI 1.04 to 1.68). Subgroup analyses did not identify any differences by gender.	expected
Cacioppo et al. (2009) review	- morbidity: cognitive decline/dementia			Research indicates that perceived social isolation (i.e. loneliness) is a risk factor for, and may contribute to, poorer overall cognitive performance, faster cognitive decline, poorer executive functioning, increased negativity and depressive cognition, heightened sensitivity to social threats, a confirmatory bias in social cognition that is self-protective and paradoxically self-defeating, heightened anthropomorphism and contagion that threatens social cohesion. These differences in attention and cognition impact on emotions, decisions, behaviours and interpersonal interactions that can contribute to the association between loneliness and cognitive decline and between loneliness and morbidity more generally.	expected
Kelly et al. (2017) review	- morbidity: cognitive decline/dementia			Evidence suggests a relationship between (1) social activity and global cognition and overall executive functioning, working memory, visuospatial abilities and processing speed but not episodic memory, verbal fluency, reasoning or attention; (2) social networks and global cognition but not episodic memory, attention or processing speed; (3) social support and global cognition and episodic memory but not attention or processing speed; and (4) CMSR and episodic memory and verbal fluency but not global cognition.	inconclusive/expected
Kuiper et al. (2015) meta-analysis	- morbidity: cognitive decline/dementia			Low social participation (RR: 1.41 (95% CI: 1.13–1.75)), less frequent social contact (RR: 1.57 (95% CI: 1.32–1.85)), and more loneliness (RR: 1.58 (95% CI: 1.19–2.09)) were statistically significant associated with incident dementia. The results of the association between social network size and dementia were inconsistent. No statistically significant association was found for low satisfaction with social network and the onset of dementia (RR: 1.25 (95% CI: 0.96–1.62). We conclude that social relationship factors that represent a lack of social interaction are associated with incident dementia. The strength of the associations between poor social interaction and incident dementia is comparable with other well-established risk factors for dementia, including low education attainment, physical inactivity, and late-life depression.	expected
Kuiper et al. (2016) meta-analysis	- morbidity: cognitive decline/dementia			Poor social relationships predicted cognitive decline; for structural (19 studies): pooled OR: 1.08 (95% CI: 1.05–1.11); functional (8 studies): pooled OR: 1.15 (95% CI: 1.00–1.32); and combined measures (7 studies): pooled OR: 1.12 (95% CI: 1.01–1.24). Meta-regression and subgroup analyses showed that the heterogeneity could be explained by the type of social relationship measurement and methodological quality of included studies.	expected
Penninkilampi et al. (2018) meta-analysis	- morbidity: cognitive decline/dementia			We included cohort and case-control studies examining the association between social engagement or loneliness and dementia risk, pooling data using a random-effects model. Poor social engagement indices were associated with increased dementia risk, including having a poor social network (RR = 1.59, 95% CI 1.31–1.96; I2 = 0.00%) and poor social support (RR = 1.28, 95% CI 1.01–1.62; I2 = 55.51%). In long-term studies (=10 years), good social engagement was modestly protective (RR = 0.88, 95% CI 0.80–0.96; I2 = 0.00%). Loneliness was associated with non-significantly increased risk (RR = 1.38, 95% CI 0.98–1.94; I2 = 45.32).	inconclusive
Cacioppo et al.	- morbidity:			We review evidence that the perception of social isolation (i.e.,	expected

(2014) review	general			loneliness) impacts brain and behaviour and is a risk factor for broad-based morbidity and mortality. However, the causal role of loneliness on neural mechanisms and mortality is difficult to test conclusively in humans. Mechanistic animal studies provide a lens through which to evaluate the neurological effects of a member of a social species living chronically on the social perimeter. Experimental studies show that social isolation produces significant changes in brain structures and processes in adult social animals.	
Cacioppo et al. (2015) review	- morbidity: neuroendocrinology			Human and animal investigations of neuroendocrine stress mechanisms that may be involved suggest that (a) chronic social isolation increases the activation of the hypothalamic pituitary adrenocortical axis, and (b) these effects are more dependent on the disruption of a social bond between a significant pair than objective isolation per se.	expected
Troya et al. (2019) review	- morbidity: self-harm			Self-harm is a major public health concern. Increasing ageing populations and high risk of suicide in later life highlight the importance of identification of the particular characteristics of self-harm in older adults. Loss of control, increased loneliness and perceived burdensome ageing were reported self-harm motivations.	expected
Choi et al. (2015) review	- morbidity: sleep, depression, fatigue			Both subjective and objective types of social isolation were associated with symptoms of sleep disturbance, depression, and fatigue in older adults. Furthermore, a few recent studies showed stronger effects of subjective social isolation than objective social isolation on sleep disturbance and depressive symptoms	expected
Chang et al. (2017) meta-analysis	- morbidity: suicidality			Eventually, across the 31 studies (203,152 participants), the overall random effect size was OR = 1.57(95% CI [1.40, 1.76]), indicating a 57% likelihood increase of suicidal ideation for elderly participants with discordant social relationships. The functional measures (OR = 1.77; 95%CI [1.48, 2.10]) of social relationships, however, were more predictive than structural measures (OR = 1.37; 95%CI [1.25, 1.51]). Among all the measures of social relationships, elderly mistreatment (OR = 2.31; 95%CI [1.81, 2.94]) had the strongest effect size, followed by perceived loneliness (OR = 2.24; 95%CI [1.73, 2.90]) and poorly perceived social support (OR = 1.59; 95% CI [1.37, 1.83]).	expected
Franklin et al. (2017) meta-analysis	- morbidity: suicidality			To provide a summary of current knowledge about risk factors of suicidality, we conducted a meta-analysis of studies that have attempted to longitudinally predict a specific STB (Suicidal thoughts and behaviours) -related outcome. The present random-effects meta-analysis produced several unexpected findings: across odds ratio, hazard ratio, and diagnostic accuracy analyses, prediction was only slightly better than chance for all outcomes; no broad category or subcategory accurately predicted far above chance levels; predictive ability has not improved across 50 years of research; studies rarely examined the combined effect of multiple risk factors; risk factors have been homogenous over time, with 5 broad categories accounting for nearly 80% of all risk factor tests; and the average study was nearly 10 years long, but longer studies did not produce better prediction.	inconclusive
Heuser et al. (2019) review	- morbidity: suicidality			It is not clear which risk factor leads to an increase in suicidal thoughts and attempts, however most studies contemplated loneliness and isolation as a covariant. A causal link between the concepts is not simple. Nevertheless, loneliness and isolation seem to be relevant factors for suicidal ideations.	inconclusive/expected
Mezuk et al. (2014) review	- morbidity: suicidality			The goal of this paper is to review and synthesize the descriptive and analytic epidemiology of suicide in long-term care settings over the past 25 years. Correlates of suicidal thoughts among long-term care residents include depression, social isolation, loneliness, and functional decline.	expected

Holt-Lunstad et al. (2015) meta-analysis	- mortality			Actual and perceived social isolation are both associated with increased risk for early mortality. The objective of this meta-analytic review is to establish the overall and relative magnitude of social isolation and loneliness and examine possible moderators. Across studies that statistically controlled for a variety of possible confounds, the independent random effects weighted average effect sizes for social isolation OR = 1.29, loneliness OR = 1.26 and living alone OR = 1.32, corresponding to an average of 29%, 26%, and 32% increased likelihood of mortality respectively. We found no differences between measures of objective and subjective social isolation. Results remained consistent across gender, length of follow-up, and world region, but initial health status influenced the findings. Results also differed across participant age, with social deficits being more predictive of death in samples with an average age younger than 65 years. Overall, the influence of both objective and subjective social isolation on risk for mortality is comparable with well-established risk factors for mortality.	expected
Rico-Uribe et al. (2018) meta-analysis	- mortality			Loneliness is a risk factor for all-cause mortality [pooled HR =1.22, 95% CI =(1.10, 1.35), p < 0.001] for both genders together, and for women [pooled HR =1.26, 95% CI =(1.07, 1.48); p =0.005] and men [pooled HR =1.44; 95% CI =(1.19, 1.76); p < 0.001] separately. Loneliness shows a harmful effect for all-cause mortality and this effect is slightly stronger in men than in women. Moreover, the impact of loneliness was independent from the quality evaluation of each article and the effect of depression.	expected
Dahlberg et al. (2022) review	- predictors of loneliness			Despite the range of factors examined in the reviewed articles, strong evidence for a longitudinal association with loneliness was found for relatively few, while there were surprising omissions from the factors investigated. Risk factors with relatively consistent associations with loneliness were: not being married/partnered and partner loss; a limited social network; a low level of social activity; poor self-perceived health; and depression/depressed mood and an increase in depression.	inconclusive/expected
Buecker et al. (2021) meta-analysis	- prevalence of loneliness			In the present preregistered cross-temporal meta-analysis, we examined whether loneliness levels in emerging adults have changed over the last 43 years. Averaged across all studies, loneliness levels linearly increased with increasing calendar years (b = .224, 95% CI [.138, .309]). This increase corresponds to 0.56 standard deviations on the UCLA Loneliness Scale over the 43-year studied period. Overall, the results imply that loneliness can be a rising concern in emerging adulthood. Although the frequently used term “loneliness epidemic” seems exaggerated, emerging adults should therefore not be overlooked when designing interventions against loneliness.	expected
Cohen-Mansfield et al. (2016) meta-analysis	- reverse connection			Variables significantly associated with loneliness in older adults were: female gender, non-married status, older age, poor income, lower educational level, living alone, low quality of social relationships, poor self-reported health, and poor functional status. Psychological attributes associated with loneliness included poor mental health, low self-efficacy beliefs, negative life events, and cognitive deficits. These associations were mainly studied in cross-sectional studies. In the focus groups, participants mentioned environmental barriers, unsafe neighbourhoods, migration patterns, inaccessible housing, and inadequate resources for socializing. Other issues raised in the focus groups were the relationship between loneliness and boredom and inactivity, the role of recent losses of family and friends, as well as mental health issues, such as shame and fear.	expected
Cuccu et al. (2021) review	- social and civic behaviour			Lonely individuals tend to be characterised by lower interpersonal trust, tend to see the world as more hostile, and expect	expected

				rejection and aggression. As such, loneliness might be contributing to the creation of a less cohesive society.	
Dykstra (2009) review	- trend of loneliness			The empirical literature on older adult loneliness is reviewed, thereby challenging three often-held assumptions that figure prominently in public debates on loneliness. The first assumption that loneliness is a problem specifically for older people finds only partial support. Loneliness is common only among the very old. The second assumption is that people in individualistic societies are most lonely. Contrary to this belief, findings show that older adults in northern European countries tend to be less lonely than those in the more familialistic southern European countries. The scarce data on Central and Eastern Europe suggest a high prevalence of older adult loneliness in those countries. The third assumption that loneliness has increased over the past decades finds no support. Loneliness levels have decreased, albeit slightly.	opposite

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