ARTICLE

the british
psychological society
promoting excellence in psychology

Loneliness, the immune system, and cardiovascular health: A systematic literature review

Antonella Granieri[1] | **Maria Domenica Sauta**[1] | **Giulia Cerutti**[1] |
Alessandra De Luca[1] | **Claudia Ricco**[1] | **Carola Grimaldi**[2] |
Marco Gonella[1,2] | **Isabella Giulia Franzoi**[1]

[1]Department of Psychology, University of Turin, Turin, Italy

[2]Psychology Unit, Local Health Authority "Città di Torino", Turin, Italy

Correspondence

Isabella Giulia Franzoi, Department of Psychology, University of Turin, via Verdi 10, 10124 Turin, Italy.
Email: isabellagiulia.franzoi@unito.it

Abstract

Objective: Loneliness can have a variety of negative effects on health, such as chronic stress, altered parasympathetic function, pro-inflammatory immune responses, and psychological distress. The aim of this systematic literature review is to investigate the effects of loneliness on health and the direct relationship between loneliness and cardiovascular health, as well as the relationship between loneliness, the immune system, and the cardiovascular system.

Methods: The review was conducted by searching Scopus, Web of Science, PubMed, PsycInfo, and PsycArticles between January 2010 and March 2025, the date of the search. We used a combination of the following keywords: (alone OR lonel* OR isolation OR exclusion OR companionship) AND (cardiovascular OR heart OR cardiac) AND (immun* OR inflamm*) AND (psych* OR mental). The quality assessment was conducted using the Critical Appraisal Checklist of the Joanna Briggs Institute.

Results: The literature search led to the identification of 23 articles. Loneliness appears to have both direct and indirect negative effects on cardiovascular health. It is associated with inflammation, which in turn affects the cardiovascular system. In addition, the associated negative feelings can have a negative impact on health as they can lead to increased inflammation and negative lifestyle habits such as alcohol consumption and nicotine use, which in turn increase inflammation.

Conclusions: From a clinical psychology perspective, it is important to consider loneliness and social isolation as indicators of fragility, which may be related to cultural

differences, an unhealthy environment, the unavailability of services, and a lack of opportunities to develop professional and social roles.

Statement of Contribution

What is already known?

- Neuroscientific and neuropsychoanalytical research confirms the central importance of the relationship between the quality of the natural and human environment in which a person lives and their psychological well-being and mental health.
- Loneliness can have a negative impact on lifestyle, leading to physical inactivity, obesity, and alcohol abuse.
- Loneliness can have a variety of negative effects on health, such as chronic stress, altered parasympathetic function, pro-inflammatory immune responses, and psychological distress.

What does this study add?

- Loneliness appear to have both direct and indirect negative effects on cardiovascular health. Is associated with inflammation, which in turn affects the cardiovascular system.
- Furthermore, loneliness appears to be associated with certain biological factors that mediate the relationship between social relationships and health, such as proteins.
- Mental health professionals are called upon to propose preventive measures aimed at improving awareness and knowledge of loneliness and its effects among young people, adults, the elderly, institutions, the community, the medical environment and the culture.

INTRODUCTION

Neuroscientific and neuropsychoanalytical researches confirm the central importance of the relationship between the quality of the natural and human environment in which a person lives and their psychological well-being and mental health (Berman et al., 2021; Das et al., 2020). The child's mind develops subjectively in a constant interplay with the affective and cognitive qualities of its caregivers and through the interpersonal relationship with them (Long et al., 2020), but the close interrelation between intrapsychic and interpersonal dimensions of the mind does not end with childhood (Brumariu & Kerns, 2022; Woodhouse et al., 2020). Even in adulthood, intrapsychic functioning, including embodied affective experiences, is profoundly influenced by the environment in which it is expressed. Even experiences such as the perception of body-related pleasure and pain, which we usually assume arise on a purely intrapsychic level, are actually shaped by interactions with other bodies and minds (Cazzato et al., 2021; Köteles, 2021).

Loneliness refers to a subjective experience of general dissatisfaction in interpersonal relationships and social contexts, together with emotional distress characterized by the subjective feeling of being alienated, ignored, or rejected by others, or, in other words, by the discrepancy between actual and

desired relationships (Klein, 1959; Winnicott, 1958; Wright, 2023). By social isolation, on the other hand, we mean the absence of interpersonal relationships and infrequent social interactions (d'Hombres et al., 2021; Galanaki, 2013). Loneliness and social isolation are often experienced together (Bell & Lawlor, 2023; d'Hombres et al., 2021). To feel socially connected, however, it is not the quantity of a person's relationships that is decisive, but the quality of the relationship experience and the satisfaction associated with it.

Loneliness and social isolation are on the rise worldwide: in 2018, 22% of adults in America, 23% in the UK, and 9% in Japan reported that they often or always feel lonely, that they lack company, that they are excluded or isolated from others, and that this has a negative impact on their lives (DiJulio et al., 2018), while in Europe, 7% of people reported that they often feel lonely (Barjaková et al., 2023). During the COVID-19 pandemic, loneliness has increased significantly (Horigian et al., 2021). A large-scale representative study by Li and Wang (2020) found an increased prevalence of loneliness (35.86%) during the COVID-19 pandemic. This finding is consistent with longitudinal data from 2221 adults, which indicates that the prevalence of loneliness more than doubled in the UK during the COVID-19 lockdown (Mental Health Foundation, 2020). The age group most affected, according to this study, is young adults. A total of 44% of 18–24 year olds reported feeling lonely during the UK's first lockdown, and almost half reported feeling anxious about it.

This is of great concern for public health, as loneliness and social isolation can have a variety of negative effects on health, such as chronic stress, increased sympathetic nervous activity, altered parasympathetic function, and pro-inflammatory immune responses (Christiansen et al., 2021; Donovan et al., 2020; Holt-Lunstad & Steptoe, 2022).

Loneliness is identified as a potential risk factor for cardiovascular disease, influencing health through multiple mechanisms (Benjamin et al., 2018; Olvera Lopez et al., 2023; Xia & Li, 2018). According to the World Health Organization (WHO, 2024), cardiovascular diseases are the leading cause of death globally, taking an estimated 17.9 million lives each year.

Loneliness is associated with both an increase and a decrease in heart rate variability (HRV), indicating altered parasympathetic function (Roddick & Chen, 2021). Loneliness affects the immune system as it leads to a chronic inflammatory state through the increase of many indicators such as fibrinogen, C-reactive protein (CRP), interleukin-6 (IL-6) (Jaremka et al., 2013), risk factors for cardiovascular disease and atherosclerotic processes. Finally, loneliness also affects other factors that are considered risk factors for cardiovascular disease, and is associated with the presence of metabolic syndrome (Henriksen et al., 2019), diabetes (Hackett et al., 2020), and elevated levels of glycated haemoglobin (HbA1c) (Shiovitz-Ezra & Parag, 2019).

There is growing evidence that immune dysregulation and inflammation underlie many cardiovascular diseases, including atherosclerosis, myocardial infarction, arrhythmias, pericardial disease, valvular heart disease, cardiomyopathies, and heart failure. Recent studies suggest that modulation of inflammation can reduce cardiovascular events. The adaptive immune system's role has shown an association with cardiovascular disease risk due to a persistent and chronic inflammatory state (Boyalla et al., 2023). Loneliness can also affect both immune and metabolic regulation by altering concentrations of inflammatory cytokines and immunoglobulins, and impairing stress circuits and cardiovascular function (Pourriyahi et al., 2021). Moreover, having few social relationships is associated with a 29% increased risk of cardiovascular disease and a 32% increased risk of stroke (Valtorta et al., 2016). Loneliness can also have a negative impact on lifestyle, leading to physical inactivity (Delerue Matos et al., 2021), obesity (Hajek et al., 2021), and alcohol abuse (Gutkind et al., 2022), and has an effect equivalent to smoking 15 cigarettes a day (Holt-Lunstad et al., 2015). Finally, it is associated with negative feelings, such as depression (Erzen & Çikrikci, 2018). On the other hand, feeling connected to others, support from a partner, and stable friendships appear to have positive effects on mortality (Becofsky et al., 2015).

In view of the link between loneliness, cardiovascular diseases, and the immune system, we decided to conduct a systematic literature review to shed light on the effects of loneliness on health and to investigate the direct relationship between loneliness and cardiovascular health as well as the relationship between loneliness, the immune system, and the cardiovascular system.

MATERIALS AND METHODS

This systematic review was registered in the PROSPERO database (ID CRD42022319384) and was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

Search strategies

The studies were identified by searching the following databases: Scopus, Web of Science, Pubmed, PsycInfo and PsycArticles. We used a combination of the following keywords: (alone OR lonel* OR isolation OR exclusion OR companionship) AND (cardiovascular OR heart OR cardiac) AND (immun* OR inflamm*) AND (psych* OR mental). Given the different search fields and the different filters available in the different databases, specific search criteria were used. The field (cardiovascular OR heart OR cardiac), which should identify the target pathology of the systematic literature review, was searched by 'abstract/title' in Scopus, by 'topic' in Web of Science, by 'title/abstract' in Pubmed, and by 'abstract' in PsycInfo and PsycArticles. The other keywords were searched for 'all text' in PsycInfo and PsycArticles and for 'all fields' in the other databases. In Pubmed, the following filters were set: 'adults' in relation to age; 'humans' in relation to the study population. For PsycInfo and PsycArticles, the following filters were set: 'adulthood' in relation to age; 'human' in relation to study population; exclusion of 'dissertations, book reviews, non-article content'.

Data analysis was performed using an Excel data extraction sheet that included (1) general study details (authors, title, journal, year of publication), (2) characteristics of the sample, (3) instruments used, and (4) main findings.

We decided to include all journal articles published in the selected databases between January 2010 and March 2025, the date of the search. In addition, only English language studies were included, although this may have missed some important outcomes and reduced the data useful to support the findings of the review. The entire process is illustrated in the PRISMA flow diagram (Figure 1).

Selection criteria

The stepwise exclusion of articles was carried out by two authors of this article [CG, MDS] who read the title, abstract and full text. In case of disagreement, a third author [IGF] was consulted.

The inclusion criteria were:

1. Quantitative original research.
2. Research explicitly addressing the experience of loneliness and isolation.
3. Research explicitly related to the cardiac and immune system.

The exclusion criteria were:

1. Research papers that do not contain original findings (literature reviews, editorials, etc.).
2. Dissertations or other research publications that are not articles.
3. Incomplete contributions (e.g., meeting abstracts).
4. Lack of explicit reference to the experience of loneliness.
5. Lack of explicit reference to the cardiac and immune system.
6. Studies that use animal models.

Any disagreement regarding the inclusion/exclusion of articles was discussed between the three researchers until agreement was reached. A list of excluded studies was maintained, indicating the level
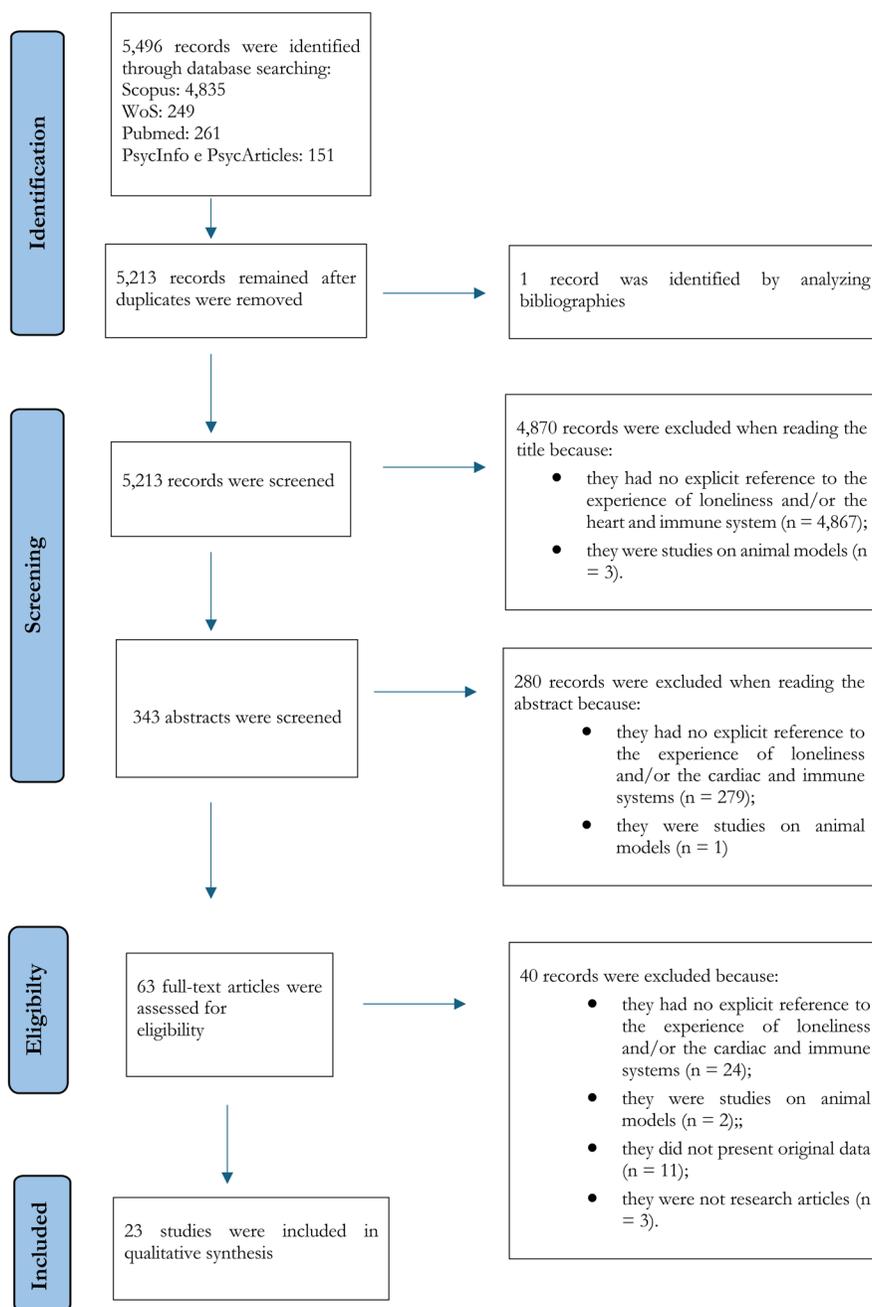
Identification

5,496 records were identified through database searching:
Scopus: 4,835
WoS: 249
Pubmed: 261
PsycInfo e PsycArticles: 151

5,213 records remained after duplicates were removed

1 record was identified by analyzing bibliographies

Screening

5,213 records were screened

4,870 records were excluded when reading the title because:
- they had no explicit reference to the experience of loneliness and/or the heart and immune system (n = 4,867);
- they were studies on animal models (n = 3).

343 abstracts were screened

280 records were excluded when reading the abstract because:
- they had no explicit reference to the experience of loneliness and/or the cardiac and immune systems (n = 279);
- they were studies on animal models (n = 1)

Eligibilty

63 full-text articles were assessed for eligibility

40 records were excluded because:
- they had no explicit reference to the experience of loneliness and/or the cardiac and immune systems (n = 24);
- they were studies on animal models (n = 2);;
- they did not present original data (n = 11);
- they were not research articles (n = 3).

Included

23 studies were included in qualitative synthesis

F I G U R E 1 Preferred reporting items for systematic reviews illustrate the study selection process.

(title, abstract or full text) and the reasons for exclusion. The bibliography of selected articles and systematic literature reviews relevant to the topic was searched for potential studies that were not found in the automatic database search. The studies identified in this step underwent the same screening process as the studies found in the database search.

Quality assessment

All papers included in the systematic review were rigorously appraised using the Critical Appraisal Checklist for Cross-Sectional, Qualitative and Randomized Controlled Trials studies (Moola et al., 2020). The Joanna Briggs Institute offers proven reliability and validity tests to assess the risk of bias of studies (Moola et al., 2020; https://jbi.global/critical-appraisal-tools). Two authors of this paper [CG, MDS] independently assessed the quality of each study. In case of discrepancies, a third author [IGF] was consulted. Disagreements regarding one article (8.33%) were resolved by discussion and consensus with the third author. Following this assessment, all articles received an acceptable quality rating for inclusion in this review. The articles were assessed using the following criteria: studies at LOW risk of bias with more than 70% 'yes' score; studies at MODERATE risk of bias with 50%–69% 'yes' score; and studies at HIGH risk of bias with less than 49% 'yes' score. As recommended in the JBI reviewer handbook, all decisions regarding the scoring system and cut-off points were approved by all reviewers before the critical appraisal process began. The assessment of the quality of the included articles is given in Table S1.

RESULTS

The automatic database search yielded a total of 5315 articles, which became 5213 after the manual elimination of duplicates. One article was identified by reading bibliographies. About 5172 articles were excluded based on the title and abstract, and 40 were excluded based on the full-text evaluation. The remaining 23 articles were analysed qualitatively (Figure 1). Table 1 summarizes the information on the studies.

Study characteristics

Nine articles were published from 2010 to 2014, seven articles from 2016 to 2022, and seven articles from 2023 to 2024. The publication of articles tended to be constant, with an average of 1/2 article per year, with the exception of 2011–2023 and 2024, when three articles were published.

We decided to include only the most recent literature in this systematic review. Therefore, as in other systematic reviews, only the last 13 years were considered (Kriakous et al., 2021; Pollard & Lee, 2003; Speroni et al., 2023). The 23 studies included in the systematic review were mostly conducted in the USA ($n = 8$, Ford et al., 2019; Heffner et al., 2011; Kapoulea et al., 2023; Kim et al., 2016; McMahon et al., 2024; Mezuk et al., 2010; Nagayoshi et al., 2014; Norman et al., 2011; Pavela et al., 2018; Putra et al., 2023; Ross et al., 2024; Yang et al., 2013), including one in collaboration with Japan (Nagayoshi et al., 2014), three in England (Hackett et al., 2012; Shankar et al., 2011; Shen et al., 2025), including one in collaboration with Sweden (Vingeliene et al., 2019) and one in collaboration with China (Liang et al., 2024), and five in Europe, namely, in: Netherlands (Brouwers et al., 2014), Finland (Kraav et al., 2021), Ireland (O'Luanaigh et al., 2012), Sweden (Djekic et al., 2020), Germany (Otten et al., 2023). Other studies were conducted in China (Li et al., 2022). In 11 articles, participants were recruited from other studies: The RAND Health and Retirement study (Pavela et al., 2018), The Multi-Ethnic Study of Atherosclerosis (Mezuk et al., 2010), The Dublin Healthy Ageing Study (O'Luanaigh et al., 2012), The English Longitudinal Study of Ageing (Shankar et al., 2011; Vingeliene et al., 2019), Framingham Offspring Study (Kim et al., 2016), The National Longitudinal Study of Adolescent to Adult Health (Ford et al., 2019), Third National Health and Nutrition Examination Survey (Yang et al., 2013), The Atherosclerosis Risk in Communities Study (Nagayoshi et al., 2014), The Pilot Swedish CArdioPulmonary bioImage Study (Djekic et al., 2020), Whitehall study II (Hackett et al., 2012), The MIDUS Refresher Biomaker and the MIDJA 2 Biomaker studies (Kapoulea et al., 2023). Three samples were from the general population (Heffner et al., 2011; Kraav et al., 2021; Norman et al., 2011),

TABLE 1 Results of the systematic review.

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
1	2012	Hackett R A., Hamer M, Endrighi R., Brydon L., Steptoe A	Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women.	Investigate the relationship between loneliness and inflammatory interleukin-6, interleukin-1 receptor antagonist and monocyte chemotactic protein-1 responses to standardized mental stress; evaluate the possible influence of variation in cortisol responses on the relationship between loneliness and inflammation.	• 543 healthy individuals. • 241 female. • Mean age female: 63.93 • Mean age male 61.18 Participants recruited from the Whitehall II study, consisting of British civil servants (study assessing acute stress response in relation to socio-economic factors and cardiovascular risk)	Higher levels of loneliness associated with greater responses of IL-6 ($p = .044$) and IL-1Ra ($p = .006$) to psychological stress and higher levels of MCP-1 ($p < .001$) in women; Elevated levels of IL-6 have been prospectively associated with coronary artery disease, and increased circulating IL-1Ra and some IL-1Ra gene polymorphisms have been linked to coronary events. No associations in men.	• Blood sample before and after stress task • Revised UCLA loneliness scale; Inflammation markers: IL-6, IL-1Ra, MCP-1	England
2	2020	Djekic, D., Fagman, E., Angerås, O., Lappas, G., Torén, K., Bergström, G., Rosengren, A.	Social support and subclinical coronary artery disease in middle-aged men and women: Findings from the pilot of swedish cardiopulmonary bioimage study	Investigate the relationship between social support and subclinical coronary artery disease.	• 1067 in healthy subjects • 492 female Age range: 50–64	Women with lower social integration and emotional attachment were more likely to have a family history of premature CVD, higher median levels of hs-CRP and leukocyte count; Social Support and CAC (Coronary artery Calcification): women with lower levels of social integration had 66.7% of no CAC; CACS> 400 was significantly higher in women with lower (6.5%) than higher levels of social support; women with lower levels of social integration had a high probability of CACS> 0; CACS>100 in women was associated with low social integration; No association between social support and CACS in men.	The Interview Schedule for Social Interaction (consisting of two subscales: social integration and emotional attachment) • Inflammation markers: HsCRP and WBC count (white Blood cell count) CACS (Coronary artery calcium scoring). Data from the Pilot SCAPIS (Swedish CArdioPulmonary bioImage Study)—study conducted between February–November 2012 to examine the association of social support with CAD (Coronary Artery Disease)	Sweden

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
3	2020	Kraav, S.-I., Awoyemi, O., Junttila, N., Vornanen, R., Kauhanen, J., Toikko, T., Lehto, S.M., Hantunen, S., Tolmunen, T.	The effects of loneliness and social isolation on all-cause, injury, cancer, and CVD mortality in a cohort of middle-aged Finnish men. A prospective study	Investigate the associations between loneliness, social isolation and mortality, and their possible underlying mechanisms.	2588 Finnish men Age range: 42–61	Loneliness predicts all-cause mortality, even after adjustments for all covariates; Loneliness predicts CVD mortality, except after adjustments for depression scores; Social isolation predicts all-cause mortality and injury mortality; The effect of social isolation on all-cause mortality was mediated by loneliness and HPL depression scores; Loneliness Positively Associated with HsCRP.	Design: prospective follow-up study of 23.2 years; Loneliness Scale and the Social Isolation Scale. Inflammation markers: Hs-CRP, CVD mortality	Finland
4	2019	Ford, J., Anderson, C., Gillespie, S., Giurgescu, C., Nolan, T., Nowak, A., Williams, K.P.	Social Integration and Quality of Social Relationships as Protective Factors for Inflammation in a Nationally Representative Sample of Black Women	Investigate the association between social relationship and inflammation.	1829 Black women aged 24–34 years	Social integration index (range 0–4 where 4=most socially integrated): 28.6% of women value 0 and 37.4% value 1; perceived quality of social relationships: 69.9% only fairly happy or dissatisfied with their romantic partners and 21.5% have no romantic partners; - no statistically significant associations emerged between level of social integration and hs-CRP categories; - Relative to perceived quality of social relationships women who reported being very happy with their romantic relationship were less likely than those who were only fairly happy or dissatisfied to have levels of hs-CRP. in the moderate to high or very high risk category; quality of parent–child relationships: in the unadjusted model, women who reported not having a mother figure were less likely than women who reported not being very close or not close at all to their mother figure to have hs-CRP levels in the moderate risk category compared to the low risk category; women who were very happy in their relationship with their romantic partner were less likely to have hs-CRP levels in the moderate, high, or very high CVD risk range.	• Berkman–Syme Social Network Index (SNI); Marker Inflammation: HsCRP. Data from the 4th wave (2007–2008) of the National Longitudinal Study of Adolescent to Adult Health.	USA

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
5	2019	Vingeliene S, Hiyoshi A, Lentjes M, Fall K, Montgomery S.	Longitudinal analysis of loneliness and inflammation at older ages: English longitudinal study of ageing	Examine associations between loneliness and biomarkers in order to identify biological pathways linking loneliness with morbidity and mortality.	• 3239 participants • Mean age 64 1777 female	Men: response to the question "most of the time during the past week, did you feel lonely?" associated with increased levels of all three biomarkers; persistent loneliness with UCLA scale associated with an increase in CRP levels; Women: The only statistically significant association is the reduction in ferritin levels with persistent loneliness	• Berkman–Syme Social Network Index (SNI); Marker Inflammation: HsCRP. • Data from the 4th wave (2007-2008) of the National Longitudinal Study of Adolescent to Adult Health. • UCLA Loneliness Scale; Marker Inflammation: fibrinogen, CRP, ferritin. Data from the English Longitudinal Study of Ageing (ELSA); waves 4 (2008/09) and 6 (2012/13); ELSA is a large population health survey of England (age>50)	Sweden-England
6	2018	Pavela G, Kim YI, Salvy SJ.	Additive effects of obesity and loneliness on C-reactive protein	Examine the independent and combined effects of obesity and loneliness on elevated C-reactive protein in older adults.	10912 non-institutionalized adults (age>51) 6428 female	Model 2 (CRP and loneliness): Men: Sometimes lonely OR 1.36(1.02–1.81). Often alone: OR 1.72(1.17–2.53). Females: Sometimes alone OR 1.24(1.01–1.52), Often alone: OR 1.38(1.11–1.72); Fully adjusted model: loneliness not associated with clinically elevated hsCRP (OR = 1.34, $p = .0535$; OR = 0.97, $p = .6776$, for men and women, respectively); In sensitivity analysis predicting logarithm-transformed hsCRP, loneliness was significantly associated with increased hsCRP among men ($b = 0.16$, $p = .0168$).	• Interviews • Loneliness measured with 11-item scale designed for large surveys; Inflammation marker: HsCRP.	USA
7	2016	Kim, D.A., Benjamin, E.J., Fowler, J.H., Christakis, N.A.	Social connectedness is associated with fibrinogen level in a human social network	Explore the relationship between a sociocentric measure of connectedness and physiological marker of stress, predicting significantly lower concentrations of fibrinogen (a biomarker of inflammation and cardiac risk).	3568 participants cohort of adult men and women	A greater social connectedness associated with substantially lower levels of fibrinogen	Marker inflammation: fibrinogen. Wave 5 (Jan. 23, 1991-June 29, 1995) of the FOS (Framingham Offspring Study) takes data from the Framingham Heart Study a prospective survey of cardiovascular disease in a large human social network	USA

(Continues)

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
8	2014	Brouwers C., Kupper N., Pelle AJ, Szabó BM, Westerhuis BL, Denollet J.	Depressive symptoms in outpatients with heart failure: importance of inflammatory biomarkers, disease severity and personality	Examine the relative importance of inflammation, disease severity and personality as predictors of depression in heart failure.	268 outpatients (diagnosed with cardiac arrest) • 66 female Mean age 66.7	NYHA classification and loneliness were independent correlates of depression before (B1) and after (B2) adjustment for socio-demographic variables; NYHA classification and loneliness were significant predictors of depressive symptoms at 12-month follow-up; Inflammation was not related to depression over time	Questionnaires administered at baseline and at follow-up after 12 months. Cytokine levels and laboratory measures taken with Blood samples at baseline; Loneliness Scale (UCLA); Markers of Inflammation: IL-6, IL-10, TNF (TNFalpha, sTNFr1, sTNFr2)	Netherlands
9	2014	Nagayoshi, M., Everson-Rose, S.A., Iso, H., Mosley, T.H., Rose, K.M., Lutsey, P.L.	Social network, social support, and risk of incident stroke: Atherosclerosis risk in communities study	Assess the association of a small social network and lack of social support with risk of stroke; evaluate the possible mediation of exhaustion and inflammation in this association.	13686 healthy Americans with no history of heart attack. • 7664 female - Mean age 57	Perceived social support was correlated with HsCRP; small social network had higher odds a higher hsCRP; participants with lack of social support had qualitatively higher, although not significantly higher, risk of stroke	• Lubben Social Network Scale; International Support Evaluation List-Short Form; Marker infiammazione: HsCRP	USA–Japan
10	2013	Yang, Y.C., McClintock, M.K., Kozloski, M., Li, T.	Social Isolation and Adult Mortality: The Role of Chronic Inflammation and Sex Differences	Assess how social isolation increases the risk of disease mortality through proinflammatory mechanisms.	6729 non institutionalized US population • 3647 female Aged >40	Harmful effects of social isolation on overall mortality Social isolation correlated with higher inflammation as measured by Crp, fibrinogen, and the inflammation index Men: 58% higher odds of high Crp for those socially isolated and 94% higher odds of being at the highest quartile of fibrinogen Females: slightly elevated Crp risks for those socially isolated that are not statistically significant, but 38% higher odds of being at the high-risk level of fibrinogen Higher inflammatory burden correlates with social isolation for both men and women, but the association is statistically significant only for men; Inflammation is highly predictive of mortality in models that simultaneously include social isolation	• Berkman–Syme Social Network Index (SNI) Marker infiammazione: CRP, fibrinogeno, serum albumin	USA

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
11	2012	O'Luanaigh C, O'Connell H, Chin AV, Hamilton F, Coen R, Walsh C, Walsh JB, Coakley D, Molloy A, Scott J, Cunningham CJ, Lawlor BA.	Loneliness and vascular biomarkers: the Dublin Healthy Ageing Study	Investigate the association between vascular disease biomarkers and loneliness in an elderly population.	466 Soggetti anziani non dementi • 258 female Mean age 75.45	Loneliness associated with elevated HbA1c levels but not with the other biomarkers (no for CRP); The lonely group had significantly higher mean BMI and Diabetes (type2) than the non-lonely group; Loneliness had a prevalence of 15.7%. When individuals with depression at the DSM case level were excluded, the prevalence of loneliness was 11.8%.	Structured semi-interviews for general information; Blood samples (non-fasting) to measure: CRP, HbA1C; Social connection measured with Wenger's Social Network; Data from Dublin Healthy Ageing Study: community-based study (cross-sectional) examining physical, psychiatric, cognitive and social health characteristics in elderly (>65 a).	Ireland
12	2011	Heffner KL, Waring ME, Roberts MB, Eaton CB, Gramling R.	Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults	Examine relationships among social isolation, C-reactive protein and coronary heart disease-death.	370 Community-based sample • 218 female Age range 40–75	Lower level of social integration had more than twice the odds of high CRP concentrations than those at the highest level of social integration; 22% of the least socially integrated individuals died of CHD during the 15-year follow-up; lowest level of social integration had more than twice the odds of death from coronary heart disease; High CRP significant predictor of death from coronary heart disease	• The PHHP Survey for social integration Marker Information: CRP	USA
13	2011	Norman GJ, Cacioppo JT, Morris JS, Malarkey WB, Berntson GG, Devries AC.	Oxytocin increases autonomic cardiac control: moderation by loneliness	Examine the role of perceived social isolation and how it moderates the effects of oxytocin on cardiac autonomic control.	40 patients with no history of mental or psychiatric illness or other chronic medical conditions; nonsmokers. 20 female	The OT (oxytocin) and placebo groups showed comparable basal levels of cytokines, hormones, and catecholamine levels; basal levels of circulating IL-6 were inversely related to HF HRV (high frequency heart rate variability); loneliness predicted significant changes in HF HRV for the oxytocin group but not for the placebo group; Loneliness did not significantly predict PEP responses to OT or placebo; CAR(cardiac autonomic regulation) reactivity negatively associated with loneliness levels within the OT(oxytocin) group but not the placebo group.	• UCLA loneliness scale HF-HRV	USA

(Continues)

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
14	2011	Shankar A., McMunn A, Banks J, Steptoe A.	Loneliness, social isolation, and behavioral and biological health indicators in older adults	Determine the impact of social isolation and loneliness on health-related behavioural and biological factors.	8688 subjects English population • 4683 female Aged >50	<2% reported being alone all the time; Nearly 7% had highest possible scores on social isolation; Both social isolation and loneliness were associated with increased risk of being inactive, smoking, as well as reporting multiple health risk behaviours; Social isolation positively associated with blood pressure, C-reactive protein, and fibrinogen levels; 30% of participants had a CRP score greater than or equal to 3 mmol/L and nearly 8% of participants had fibrinogen levels greater than 4 g/L associated with increased risk of cardiovascular disease; Older age was associated with greater social isolation and loneliness. Women showed higher scores on loneliness; Loneliness not significantly associated with blood pressure; Increases in social isolation associated with small and significant increases in blood pressure; Scores on loneliness were not correlated with CRP or fibrinogen levels; Social isolation showed small positive associations with either CRP.	• Revised UCLA Loneliness Scale; • Social isolation index; Inflammation markers: CRP and fibrinogen; Blood pressure measurement.	England
15	2010	Mezuk, B., Diez Roux, A.V., Seeman, T.	Evaluating the buffering vs. direct effects hypotheses of emotional social support on inflammatory markers: The Multi-Ethnic Study of Atherosclerosis	Evaluate the association of social support with inflammatory markers associated with cardiovascular risk factors—namely C-reactive protein, interleukin-6 and fibrinogen—with two competing models (low social support associated with inflammation; high social support buffering the effects of stress on inflammation).	6153 subjects • 3224 female Age range 45–84	Low ESS (Emotional Social Support) associated with: prevalence of both recent and chronic stress; mean levels of all inflammatory markers were higher although this pattern was statistically significant only for fibrinogen; mean levels of inflammatory markers higher in women than in men and increased with age; Direct Hypothesis(ESS-Inflammation): low ESS significantly associated only with CRP (after all adjustments) in men; Buffer Hypothesis: in middle-aged women high ESS moderates stress-CRP effect. married people have higher social emotional support and that the values of perceived social emotional support and levels of inflammation (CRP, fibrinogen and IL-6) varied significantly with marital status ($p > .001$)	• Social emotional support index (ESSI); • Markers: CRP, IL-6 and fibrinogen. Data from the baseline interview of the Multi-Ethnic Study of Atherosclerosis (MESA sample); study of predictors of subclinical cardiovascular disease; (2000-2002)	USA

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
16	2023	Kapoulea EA; Ready RE; Ginn JC.	Loneliness and risk for cardiovascular disease in the United States and Japan: The effects of nationality, collectivism, and gender	Examine if nationality, collectivism and gender have an impact on the associations between loneliness and cardiovascular disease.	937 participants-aged 36 to 78 – 458 men and 479 women. From United States: man (323); women (3219); from Japan: men (135); women (158)	The study found significant interactions of (1) nationality and gender on metabolic dysregulation (MetD) and inflammation, (2) gender and loneliness on sleep dysfunction, and (3) nationality and loneliness on MetD. Loneliness was associated with greater MetD in the U.S. but not in Japan. Loneliness was prevalent in the U.S. (25.39%) and Japan (20.82%). Japanese adults had significantly lower MetD, inflammation than US adults (ps < .0125). Women had significantly lower BP and MetD, and higher inflammation than men (ps < .001). We found a significant interaction between gender and nationality, such that the effect of nationality on MetD was higher in men than women ($b = −0.08$, SE = 0.02, $p < .001$). The interaction between gender and nationality was significant, such that the effect of nationality on inflammation was higher in men than women ($b = −0.49$, SE = 0.09, $p < .001$).	Loneliness was measured by the Center for Epidemiological Studies Depression Inventory (CES-D; Radloff, 1977). Collectivism was measured with the interdependent subscale of Singelis' Self-Construal Scale (SCS; Singelis, 1994). Participants completed the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-report measure of sleep in the past month (Buysse et al., 1989). All data (physical health, blood draws, and a physical exam) were collected at the Biomarker Visit	USA
17	2022	Li H.; Li S.; Yang H.; Zhang Y.; Xu F.; Cao Z.; Ma Y.; Hou Y.; Borne Y.; Wang Y.	Association of comprehensive mental health with incident cardiovascular disease: A prospective cohort study	Investigate associations between mental health status and cardiovascular disease.	339,616 participants, 186,474 female-aged 40 to 69 years	A statistically significantly increased risk of incident CVD was observed for the four mental factors individually (depressive symptoms, anxiety, loneliness, and neuroticism), with adjusted hazard ratios ranging from 1.03 to 1.44. (Loneliness HR= 1.22, CI 1.18, 1.26). The composite score of such four mental factors also positively associated with CVD risk in a dose-response manner, with the highest scores associated with a 1.56-fold (95% confidence interval 1.47 to 1.65), 1.61-fold (1.51 to 1.72), and 1.44-fold (1.25 to 1.67) higher CVD, CHD, and stroke risk, respectively	Depressive symptoms were assessed using a 2-item depression scale (PHQ-2), and anxiety using a 2-item general anxiety disorder (GAD)−2. Feelings of loneliness were assessed on the basis of responses to the following yes-no question: "Do you often feel lonely?". Neuroticism was measured via 12-item Eysenck Personality Questionnaire Revised-Short Form. Physical health examinations.	China

(Continues)

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
18	2024	Liang YY.; Zhou M.; He Y.; Zhang W.; Wu Q.; Luo T.; Zhang J.; Jia F.; Qi L.; Ai S.; Zhang J.	Observational and genetic evidence disagree on the association between loneliness and risk of multiple diseases	Examine the associations between loneliness and non-overlapping diseases.	In the current study sample from the UK Biobank the mean age was 56.5 years, 259,806 (54.6%) out of 476,100 participants were women.	Compared with individuals who did not experience loneliness, those who experienced loneliness had the greatest risk of developing **diseases of the circulation system** (HR=1,18, CI 1,16–1,21): ischemic heart disease HR=1, 29 (CI 1,24–1,34); stroke HR=1,25 (CI 1,16–1,36); atrial fibrillation HR=1,21 (CI 1,15–1,28); peripheral arterial disease HR=1,45 (CI 1,33–1,59); Hypertension HR=1,20 (CI 1,17–1,23). To describe the disease burden of loneliness, we computed the 10-year cumulative incidence rate (CIR) for the 14 disease categories among individuals in the UK Biobank experiencing loneliness: CIR for circulatory diseases was 335 per 1,000 persons. **Inflammatory factors** were also potential explanatory factors for loneliness–disease associations, with the PERM range of 2%–18%: ischemic heart disease (HR=1,44, CI 1,38–1,50, PERM 10%); Stroke (HR=1,38, CI 1,27–1,49, PERM 10%); atrial fibrillation (HR=1,31, CI 1,24–1,38, PERM 11%); peripheral arterial disease (HR=1,84, CI 1,68–2,01, PERM 11%); Hypertension (HR=1,31, CI 1,28–1,34, PERM 11%).	-**Loneliness** was assessed through the administration of three items: "Not Lonely", "Lonely", "Usually able to confide". -**Inflammatory factors** measured were: leucocytes, platelets, platelet crit, lymphocytes, monocytes, neutrophils, eosinophils, basophils, C-reactive protein	UK, China

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
19	2025	Shen, C; Zhang, RH; Yu, JT; Sahakian, BJ; Cheng, W; Feng, JF	Plasma proteomic signatures of social isolation and loneliness associated with morbidity and mortality	Underline the biology underlying the connection between social relationship and health, by characterizing the proteomic signatures of social isolation and loneliness.	Our primary study population included 42,062 participants (aged 56.4 ± 8.2 years, 52.3% female) from the UK Biobank	Growth differentiation factor 15 (GDF15), a protein belonging to the transforming growth factor-β superfamily that acts as an inflammatory marker, demonstrated the strongest association with social isolation (OR = 1.22, 95% CI 1.17 – 1.27, $p = 1.2 \times 10^{-19}$). C-X-C motif chemokine ligand-14 (CXCL14), an immune and inflammatory modulator, emerged as the second most significant protein associated with social isolation (OR = 0.84), (95% CI 0.81-0.88, $p = 2.4 \times 10^{-17}$). we delved into the potential mediating role of proteins, which have been implicated as causally linked to loneliness, in the relationship between loneliness and health outcomes. Effects were observed for cardiovascular diseases (percentage of excess risk mediated-PERM 5.6–8.3%). ADM emerged as the primary mediator linking loneliness to various health outcomes, including CVD (8.3%). All five proteins (GFRA1, ADM, FABP4, TNFRSF10A and ASGR1) significantly mediated the association between loneliness and CVD, stroke and mortality after Bonferroni correction.	**Social isolation** was assessed through three dichotomous questions (living alone (1 = yes), social contact (1 = less than monthly) and participation in social activities (1 = less than weekly)), with an individual defined as socially isolated if scoring 2 or 3. **Loneliness** was evaluated using two binary items akin to questions in the revised UCLA loneliness scale: often feeling lonely (1 = yes) and frequency of confiding in close people (1 = less than once every few months). An individual was classified as lonely if scoring 2. **Plasma proteins** were derived from blood collection	UK

(Continues)

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
20	2024	McMahon G.; Howard S.; Manunta E.; Griffin S.; Bradshaw D.; Nightingale A.; Muldoon O.T.	Social group membership and biomarkers of health	Address the influence of group on biological health outcomes, by examining the effects of belonging to a social group on cardiovascular and cortisol reactivity to stress.	213 healthy adults participants-aged 18 to 55 – 123 men and 90 women	The results suggest that social group membership allows for better cardiovascular adaptation and a healthier stress response; There is also a higher physiological stress tolerance, which suggests better physical resilience to psychological stress. This indicates that having a social network could improve physical health and stress tolerance in the long run. Results indicated a positive association between social group membership and SBP reactivity (β = .17, t = 2.45, p = .014, [1.03, 9.07]) and DBP reactivity (β = .14, t = 2.10, p = .037, [14, 4.44]), but not HR reactivity (β = .09, t = 1.32, p = .189, [−1.06, 5.31]), in response to the speech task. The positive associations indicated higher levels of CVR in participants who reported being members of a social group for the speech task. Specifically, the participants who reported being a member of a social group showed better SBP adaptation from the speech task (M = 23.68, SD = 13.26) to the maths task (M = 19.69, SD = 13.33), whereas in comparison, people who were not members of any social group showed less reduction in reactivity from the speech task (M = 18.69, SD = 13.76) to the maths task (M = 17.42, SD = 13.53). In other words, for those who belonged to a social group, SBP reactivity decreased throughout the stress period, which is indicative of successful cardiovascular stress-response adaptation.	Social Network Index is a psychometric tool used to measure an individual's social network, focusing on the quantity and quality of their social connections. Critikon Dynamap Monitor is used to measure systolic and diastolic blood pressure and heart rate. Cortisol is measured as a biomarker of stress and it can be assessed using saliva, blood, or urine samples.	USA

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
21	2024	Ross E.J.; Jimenez D.E.; Ghanooni D.; Mendez A.; Hirshfield S.; Horvath K.J.; DeVries B.; Dilworth S.E.; Carrico A.W.; Martinez C.A.	Loneliness, Methamphetamine Use, and Cardiovascular Risk Factors Among Sexual Minority Men in the COVID-19 Era	Examine the associations of loneliness, stimulant use and cardiovascular risk in sexual minority men with and without HIV.	103 SMM participants (sexual minority men)-18 years	Loneliness was found to have a negative relationship with total cholesterol and LDL levels in the cardiometabolic subgroup ($n = 56$). In addition, men from sexual minorities (SMM) who used methamphetamine ($t(101) = 2.03, p < .05; d = 0.42$) and those who tested positive for a stimulant use disorder ($t(101) = 2.07, p < .05; d = 0.46$) had significantly higher mean loneliness scores. Linear regression analyses showed that loneliness was negatively correlated with LDL and total cholesterol levels, but this relationship was only observed among the MSMs who had used methamphetamine.	UCLA Loneliness Scale or Social Isolation Scale used to measure loneliness, consisting of 10 questions on a 4-point Likert scale that asks a series of questions like "How often do you feel close to people?" Critikon Dynamap Monitor to measure blood pressure; electrocardiogram to measure heart rate HIV-negative status was measured by the Oraquick ADVANCE ® HIV-1/2 rapid antibody test. Analysis of biological samples (blood, saliva, urine) to determine levels of cortisol, C-reactive protein (CRP), or other inflammation-related biomarkers. The ASSIST test (Alcohol, Smoking and Substance Involvement Screening Test) is a screening tool to also detect problematic methamphetamine use.	USA

(Continues)

TABLE 1 (Continued)

ID	Year	Authors	Title	Aim	Sample	Main results	Measures	Nation
22	2023	Otten D.; Ernst M.; Werner A.M.; Tibubos A.N.; Reiner I.; Brähler E.; Wiltink J.; Michal M.; Nagler M.; Wild P.S.; Münzel T.; König J.; Lackner K.J.; Peiffer N.; Beutel M.E.	Depressive symptoms predict the incidence of common chronic diseases in women and men in a representative community sample	Predict chronic disease based on depressive symptoms and test sex-dependent effects.	N=12,285 - age of 54.4 - 6005 women (48.9%) and 6280 men (51.1%).	The results show that depressive symptoms predict the incidence of cardiovascular disease (CVD) (OR=1.06; p=.003). However, associations with cardiovascular disease in men (p=.065) did not reach significance.	Patient Health Questionnaire-9 (PHQ-9): for depressive symptoms. self-report for sociodemographic variables. Loneliness was assessed by an item "I am often alone/ have few contacts. Blood glucose, measured by HbA1C. Hypertension assessed by mean systolic blood pressure	Germany
23	2023	Putra I.G.N.E.; Daly M.; Sutin A.; Steptoe A.; Robinson E.	Psychological Pathways Explaining the Prospective Association Between Obesity and Physiological Dysregulation	Test whether psychological measures explain why obesity is associated with physiological dysregulation, measuring cardiovascular, immune system and metabolic function.	Age >50years- Participants in both studies were similar in age and gender. In the HRS group, there was a higher percentage of participants with obesity and non-white people. English Longitudinal Study of Ageing (ELSA, study 1): 6.250 participanti. Health and Retirement Study (HRS, study 2): 9,664 partecipanti.	Study 1, which examined the link between obesity and physiological dysregulation in the context of an English longitudinal study on ageing, identified the role of some psychological variables as mediators in this relationship. Physiological dysregulation, when evaluated through the number of biomarkers, showed no significant mediation by psychological variables, such as loneliness. Single-mediation analyses of psychological measures in Study 2 did not suggest any significant mediation by underlying psychological factors in the association between obesity and physiological dysregulation.	ELSA Study: Body Mass Index (BMI) calculated using data on weight and height collected during health assessments and biomarkers. Health assessments: these measurements included biomarkers and other physical assessments. Psychological factors: A wide range of psychological measures was collected in wave 4 (2008–2009), but the text does not specify which psychological tools were used exactly. HRS study: Biomarkers: cholesterol, blood sugar and blood pressure measurements. Psychological measures: Psychological measurements were collected from 2006 (Wave 8) onwards, using standardized psychological measurement tools. The text does not specify which instruments. Physical measurements: measurement of blood pressure, weight and height to calculate the BMI, and other biological biomarkers.	The United Kingdom (study 1) and United States (study 2)

while one study recruited outpatients diagnosed with cardiac arrest (Brouwers et al., 2014). The studies identified were predominantly longitudinal in design ($n = 8$; Brouwers et al., 2014; Kim et al., 2016; Kraav et al., 2021; Mezuk et al., 2010; Nagayoshi et al., 2014; Pavela et al., 2018; Putra et al., 2023; Shen et al., 2025; Vingeliene et al., 2019; Yang et al., 2013), three were observational studies (Liang et al., 2024; Otten et al., 2023; Ross et al., 2024), eight were cross-sectional (Djekic et al., 2020; Ford et al., 2019; Hackett et al., 2012; Kapoulea et al., 2023; McMahon et al., 2024; O'Luanaigh et al., 2012; Shankar et al., 2011), one of which included a placebo control group (Norman et al., 2011), and two were case-cohort studies (Heffner et al., 2011; Li et al., 2022).

The variables involved in the studies were measured using self-report measures of the experience of loneliness, blood tests for inflammatory markers and blood pressure, the presence of atherosclerosis and previous cardiovascular disease in terms of cardiac function. The sample size ranges from 40 (Norman et al., 2011) to 13,686 people (Nagayoshi et al., 2014). The age range is 24–84 years. Three studies (Ford et al., 2019; Norman et al., 2011; Ross et al., 2024) were conducted on a sample of young adults (aged 24–34 years), while the other studies (Brouwers et al., 2014; Djekic et al., 2020; Hackett et al., 2012; Heffner et al., 2011; Kapoulea et al., 2023; Kim et al., 2016; Kraav et al., 2021; Li et al., 2022; Liang et al., 2024; Mezuk et al., 2010; Nagayoshi et al., 2014; O'Luanaigh et al., 2012; Otten et al., 2023; Pavela et al., 2018; Putra et al., 2023; Shankar et al., 2011; Shen et al., 2025; Vingeliene et al., 2019; Yang et al., 2013) were conducted on middle-aged or older people (aged 40–84 years). One study was conducted on a group of young and middle-aged people (aged 18–55 years).

Only two of the 23 studies were conducted on an all-female (Ford et al., 2019) or all-male (Kraav et al., 2021; Ross et al., 2024) sample.

Qualitative synthesis

The results of the articles were grouped into 12 categories according to their specific focus (each article could be grouped into more than one category if relevant): (1) The direct relationship between loneliness and the cardiac system (8 articles); (2) The role of the immune system in the relationship between loneliness and the cardiac system (14 articles); (3) Loneliness and risk factors for the cardiac and immune system (10 articles); (4) Loneliness and lifestyles affecting health (8 articles); (5) Loneliness and sleep (2 articles); (6) Loneliness and depression (4 articles); (7) Loneliness, oxytocin, and the cardiac system (1 article); (8) Marital status and the relationship between loneliness and health (3 articles); (9) Relationships and health (3 articles); (10) Nationality, gender, and risk factors for the cardiac and immune system (1 article); (11) Depression and the cardiac system (2 articles); (12) The role of proteins in the relationship between social isolation, loneliness, and the cardiac system (1 article).

The assessment using the Joanna Briggs Institute checklist (Moola et al., 2020; https://jbi.global/critical-appraisal-tools) showed that all articles received an acceptable quality rating for inclusion in this review. Nine (60%) studies were cross-sectional and six (40%) were cohort studies. All nine cross-sectional studies assessed were at low risk of bias. Of the six cohort studies assessed, four articles had a low risk of bias and two had a moderate risk of bias.

The direct relationship between loneliness and the cardiac system

Five studies investigated the relationship between loneliness, social isolation and the cardiovascular system. Kraav et al. (2021) reported that only loneliness predicted mortality from cardiovascular disease, except in the model adjusted for depression scores. Consistently, in the studies performed by Li et al. (2022) and by Liang et al. (2024), a statistically significantly increased risk of developing cardiovascular diseases (Li et al., 2022) and diseases of the circulatory system (Liang et al., 2024) was observed in subjects who reported loneliness. Shankar et al. (2011) showed that loneliness did not correlate with blood pressure, while social isolation was slightly associated with a small increases in

blood pressure (systolic and diastolic). In terms of blood pressure, the study by O'Luanaigh et al. (2012), in which the sample was divided into 'lonely' and 'not lonely' groups based on their response to the question 'Do you feel lonely?', reported that both groups had systolic hypertension.

Two studies have investigated the relationship between social isolation and the heart. The case-cohort study by Heffner et al. (2011) reported that 22% of those with lower levels of social integration died of coronary heart disease during the follow-up period (15 years). Those with lower levels of social integration were more than twice as likely to die from coronary heart disease as those with the highest levels of social integration. High levels of social isolation correlated with an increased risk of dying from cardiovascular disease, as reported in the study by Yang et al. (2013).

One study examined the relationship between social support and the cardiac system. Djekic et al. (2020) reported that women with lower social support were more likely to have a family history of premature CVD and a higher risk of CAD; and those with lower social integration have a 'vascular age' higher by about 14 years, that is, 50-year-old women with low integration and 64-year-old women with moderate social integration have the same prevalence of CACS >0.

The role of the immune system in the relationship between loneliness and the cardiac system

Four studies have reported a link between loneliness and inflammation as measured by indicators such as C-reactive protein, fibrinogen, interleukins and ferritin, lymphocytes, leucocytes and monocytes, all of which are risk factors for cardiovascular disease. Worthy of note, the study by Pavela et al. (2018) found no significant correlations between C-reactive protein levels and loneliness, whereas in a sensitivity analysis, loneliness levels were associated with increased high-sensitivity C-reactive protein (HsCRP) in men. Hackett et al. (2012) reported that loneliness was associated with increased levels of inflammation (particularly higher levels of IL-6, IL-1Ra, and MCP-1) in women (independent of age, occupational status, BMI, and smoking status). Liang et al. (2024) showed that inflammatory components (leucocytes, platelets, platelet crit, lymphocytes, monocytes, neutrophils, eosinophils, basophils, C-reactive protein) were potential explanatory factors for the association between loneliness and cardiovascular diseases. In the study by Vingeliene et al. (2019), different results were reported depending on gender: men who had high levels of loneliness at follow-up also had elevated levels of all three inflammatory indicators; onset of loneliness and persistent loneliness were positively associated with increased C-reactive protein. In women, however, there was a statistically significant negative association between prolonged loneliness and ferritin levels. In contrast to the studies presented so far, the study by O'Luanaigh et al. (2012) found no association between loneliness and inflammation levels (CRP).

Two studies have examined loneliness and isolation in relation to inflammation, and the data are contradictory. The study by Kraav et al. (2021) reported that loneliness was positively correlated with levels of HsCRP, while it found no association with social isolation. Contrasting results were found in the study by Shankar et al. (2011), in which social isolation was positively associated with C-reactive protein and fibrinogen, while loneliness was not associated with an increase in these indicators.

The study by Yang et al. (2013) reported on the impact of social isolation on inflammation; specifically, social isolation negatively impacted overall mortality and was positively correlated with higher levels of inflammation (as measured by CRP, fibrinogen, and the inflammatory index); socially isolated men were 58% more likely to have elevated levels of C-reactive protein and 94% more likely to have higher levels of fibrinogen; social isolation was positively correlated with inflammatory burden and had an impact on mortality (inflammation-mediated effect). Socially isolated women were 38% more likely to have high fibrinogen levels.

One study reported that social isolation was associated with increased leucocyte and fibrinogen levels, but not CRP levels (Kraav et al., 2021).

Two studies have found an association between social integration and inflammation. The case cohort of Heffner et al. (2011) showed that individuals with lower social integration were more than twice as likely to

have high CRP levels than those with higher social integration and that high CRP levels were a significant predictor of death from coronary heart disease (CHD). In the study by Ford et al. (2019), no association was found between social integration and inflammation (HsCRP markers). However, an important finding emerged for relationship quality (assessed by indicating the level of happiness in the current romantic relationship and the perceived closeness of the mother and/or father figure), which was significantly negatively associated with inflammation. In particular, women who were happy in their romantic relationship and were fairly/very close to the maternal figure were less likely to have elevated levels of inflammation (HsCRP).

Three studies have examined the relationship between inflammation and social support. The study by Mezuk et al. (2010) showed that lower levels of social-emotional support were significantly associated with increased fibrinogen levels. On average, women had higher inflammation levels, which increased with age. In men, there was a negative association between the level of emotional support and C-reactive protein levels, while in women aged 45–64 years, a high level of emotional social support positively influenced and reduced the association between high stress and CRP. The cross-sectional study by Djekic et al. (2020) showed that only women with low levels of social support had higher white blood cell counts and higher mean HsCRP levels. The longitudinal study by Nagayoshi et al. (2014) reported that the concentration of HsCRP correlated with the perceived value of social support, but not with the value of the social network. However, individuals with a small social network were more likely to have high levels of HsCRP.

The study by Kim et al. (2016) reported that social connectedness was associated with fibrinogen levels, with higher social connectedness being associated with lower fibrinogen levels (higher levels in women) and the latter increasing with age.

Loneliness and risk factors for the cardiac and immune system

A study by Djekic et al. (2020) reported that women with low social support had higher average triglyceride levels and lower average HDL cholesterol levels.

Two studies examined the impact of support, social integration, and loneliness on glycated haemoglobin and diabetes. Women with low levels of social support had higher mean glycated haemoglobin (HbA1c); in both sexes, low levels of social integration were associated with the presence of diabetes mellitus (Djekic et al., 2020). Similar results were obtained in the study by O'Luanaigh et al. (2012), who found a significant positive association between the degree of loneliness and glycated haemoglobin (HbA1c). Normally, glycated haemoglobin is used as an indicator of the presence of diabetes and is therefore correlated with diabetes, but in this study, the association also existed in the non-diabetic group and was therefore independent of diabetes. Finally, the group categorized as 'lonely' had a significantly higher average prevalence of type 2 diabetes than the group categorized as 'not lonely' (15% vs. 8.2%). Kapoulea et al. (2023) reported an association between loneliness and metabolic dysregulation (MetD) (measured by blood pressure, HDL levels, body mass index, and waist circumference), which in turn can be considered a risk factor for the cardiac system. In contrast, Ross et al. (2024) found that loneliness was negatively correlated with LDL and total cholesterol levels, but this association was only observed in sexual minority men who had used methamphetamine. The study by Nagayoshi et al. (2014) found that people with a small social network (compared with people with more social contacts) were more likely to develop diabetes (19.1% vs. 14.5%). However, this association was not found in the studies by Pavela et al. (2018), Mezuk et al. (2010), and Heffner et al. (2011).

Finally, one study (Hackett et al., 2012) reported on the association between loneliness and cortisol: in women, cortisol levels after stress were inversely associated with the degree of loneliness, and the cortisol response had no effect on the positive association between loneliness and inflammation.

Loneliness and lifestyles that affect health

Four studies have reported on the effects of loneliness, isolation and social support on body mass index. O'Luanaigh et al. (2012) conducted a cross-sectional study in which the sample was divided into two

groups based on the response to the following question 'Do you feel lonely?' from the CES-D (Centre for Epidemiologic Studies Depression Scale) (Radloff, 1977). The results show that the lonely group had a significantly higher mean body mass index than the non-lonely group. Other behaviours such as alcohol consumption, smoking and physical activity were also examined, but no significant differences were found between the two groups.

Djekic et al. (2020) found that only women with low levels of social support were more likely to have a higher mean body mass index and a larger waist circumference. In the study by Vingeliene et al. (2019), men who felt lonely were more likely to be underweight or obese. A similar result was seen in the study by Kraav et al. (2021), which found that social isolation was positively associated with body mass index. This study also analysed the effect of loneliness, which was positively associated with alcohol consumption. In contrast, the study performed by Putra et al. (2023) did not suggest any significant mediation by loneliness in the association between obesity and physiological dysregulation, measured through biomarkers such as cholesterol, blood sugar, and blood pressure. Two studies reported that people with a small social network were more likely to be smokers (35.9% vs. 20.3%) (Nagayoshi et al., 2014) and people with low social support were more likely to become smokers (Mezuk et al., 2010).

Finally, three studies reported that loneliness and isolation were associated with smoking and lower physical activity. Shankar et al. (2011) examined the impact of feelings of loneliness and social isolation and reported that an increases in both feelings of loneliness and social isolation was associated with an increased likelihood of being a smoker and/or being physically inactive (results were stronger for social isolation); when comparing the two measures, the authors found that a one standard deviation increase in loneliness and social isolation scores was associated with a 10% and 32% increased likelihood of being a smoker, 13% and 23% increased likelihood of being physically inactive, and 16% and 56% increased likelihood of engaging in both behaviours. Similar results were found in the study by Djekic et al. (2020); in particular, low levels of social integration in men were associated with smoking (in both sexes) and physical inactivity, low levels of emotional attachment with smoking in men and with smoking and physical inactivity in women. The same result was seen in the study by Kraav et al. (2021), which emphasized that loneliness and social isolation were negatively associated with physical activity.

Loneliness and sleep

Two studies investigated the effects of loneliness on sleep quality and quantity. Specifically, Kraav et al. (2021) reported that both feelings of loneliness and social isolation were negatively correlated with sleep quantity, while Kapoulea et al. (2023) found an interaction between loneliness and sleep disturbance as measured by the Pittsburgh Sleep Quality Index (PSQI).

Loneliness and depression

Two studies have investigated the link between loneliness and depression. The study by Brouwers et al. (2014), conducted in a group of outpatients with heart failure, examined the association between loneliness and depressive symptoms at baseline and at follow-up (after 12 months) and found that loneliness was significantly associated with depression at baseline and was a significant predictor of depressive symptoms at follow-up.

In the study by O'Luanaigh et al. (2012), they reported a prevalence of loneliness of 15.7%, which dropped to 11.8% after excluding those diagnosed with depression.

Two studies have investigated the relationship between loneliness, isolation, and depression. Kraav et al. (2021) showed a positive correlation between loneliness, social isolation and levels of depression (a correlation that was stronger for loneliness), and depression influenced the association between loneliness and cardiovascular disease mortality. The study by Shankar et al. (2011), using data from the English Longitudinal Study of Ageing (ELSA: cross-sectional survey of the health of the English

population), found that both loneliness and social isolation were positively correlated with depression; however, the positive association between social isolation and loneliness was reduced in the model adjusted for age, gender and depression.

Loneliness, oxytocin and the cardiac system

One study investigated the effect of oxytocin on cardiac autonomic control and its association with loneliness. Norman et al. (2011). Oxytocin led to a significant increase in high heart rate variability (HRV) and reduced the pre-ejection period. However, regression analysis revealed that subjects with high levels of loneliness were less sensitive to the effects of oxytocin on HRV and total cardiac autonomic regulation index.

Marital status and the relationship between loneliness and health

Three studies have examined the role of marital status. In particular, the results of Mezuk et al. (2010) showed that married people have higher social-emotional support and that the levels of perceived social-emotional support and inflammation (CRP, fibrinogen and IL-6) varied significantly with marital status. However, in multivariate regression analyses, the relationship between stress and inflammation was not significantly modified by marital status. Shankar et al. (2011) reported that the association between social isolation and blood pressure, C-reactive protein and fibrinogen was no longer significant when the marital status variable was excluded from the analysis, suggesting that this effect was due to the marital status variable. However, these results were not found in the study by Kraav et al. (2021).

Relationships and health

One study (Heffner et al., 2011) examined the association between the individual components of the social integration index (unmarried, contact with family/friends, religious affiliation, voluntary participation in community groups) and mortality due to CRP and CHD and reported that religious affiliation and voluntary participation in groups were negatively associated with CHD mortality in the unadjusted (regression) model (for age and other control variables).

One study examined the association between relationship quality and inflammation; in particular, the results of the analysis by Ford et al. (2019) reported that women who described themselves as very happy with their romantic relationship were less likely to have elevated levels of HsCRP (compared with those who described themselves as fairly happy or unhappy); women who reported being fairly/very close to their mother or not having a mother figure were less likely to have elevated levels of HsCRP (risk for CVD) than those who reported not being close to their mother figure. No significant data were found between father figure and HsCRP levels.

Another study investigated the interaction between social group membership and cardiovascular adaptation. McMahon et al. (2024) showed that having a social network could improve physical health and stress tolerance, as they found a positive association between social group membership and systolic blood pressure reactivity and diastolic blood pressure reactivity (but not heart rate reactivity) measured in response to a stress task.

Nationality, gender and risk factors for the cardiac and immune system

One study examined the interactions of nationality and gender on metabolic dysregulation (MetD) and inflammation. In particular, Kapoulea et al. (2023) showed that Japanese adults had significantly lower

MetD and inflammation than US adults. As far as gender is concerned, women reported significantly lower blood pressure and MetD, but higher inflammation than men.

Depression and cardiac system

Two studies investigated the role of depressive symptoms in predicting the incidence of cardiovascular diseases. The analyses performed by Li et al. (2022) and by Otten et al. (2023) suggested that the presence of depressive symptoms can be associated with a statistically significantly increased risk of incident cardiovascular diseases.

The role of proteins in the relationship between social isolation, loneliness and cardiac system

One study focused on the causal relationship between proteins and loneliness and delved into the potential mediating role of proteins, which have been implicated as causally linked to loneliness, in the relationship between loneliness and health outcomes. Shen et al. (2025) reported that the five proteins (GFRA1, ADM, FABP4, TNFRSF10A, ASGR1), which were causally linked to loneliness, significantly mediated the association between loneliness and cardiovascular diseases, stroke, and mortality.

DISCUSSION

This is the first systematic literature review that analyses the relationship between loneliness, the cardiac system, and the immune system and shows how loneliness primarily affects the cardiac system either directly or indirectly. The scientific statement from the American Heart Association highlights the need for more data on strategies to improve cardiovascular health for people who are socially isolated or lonely, as well as more robust evidence showing how these experiences affect brain health.

Regarding the direct pathway, loneliness and isolation appear to be associated with cardiovascular disease mortality (Alcaraz et al., 2019; Stringhini et al., 2018) and elevated systolic blood pressure (Hawkley et al., 2006), while living alone is associated with a higher risk of CVD (Chen et al., 2024).

The indirect pathway works in several ways (Yang et al., 2022).

Loneliness appears to be associated with inflammation, which in turn affects the cardiac system and in particular increases the levels of many inflammatory indicators (fibrinogen, CRP, IL-6) (Jaremka et al., 2013). It is also associated with risk factors for the heart and immune system, such as elevated glycated haemoglobin levels (Stokes & Carr, 2020), an increased likelihood of diabetes, and elevated cholesterol levels (Richard et al., 2017), and an increase in cortisol (Doane & Adam, 2010). Furthermore, loneliness appears to be associated with certain biological factors that mediate the relationship between social relationships and health, such as proteins (Hodgson et al., 2020). Loneliness appears to lead to negative lifestyle choices, such as dysregulated eating, alcohol consumption, nicotine use, and lack of physical activity— all factors that increase inflammation and are less conducive to health.

In literature, several studies show mixed achievements regarding the relationship between loneliness and obesity and the cardiac system: some results showed that social isolation was significantly associated with CVD-related mortality in people with obesity.

It is already known that social support is strongly linked to a reduced risk of CVD (Singh et al., 2023; Teshale et al., 2023; Freak-Poli et al., 2021;). Social interaction and social support can reduce stress, promote healthy behaviours, provide emotional support, and reduce CVD risk through positive social engagement; social isolation can weaken these protective factors, leading to an increased risk of CVD (Zheng et al., 2023; Zhou et al., 2024); other studies, however, show no relationship between loneliness, obesity, and the cardiac system, attributing the existing connection between obesity and heart problems

solely to biological factors (Teshale et al., 2023; Vasan et al., 2024). This discrepancy would require further studies that emphasize the influence that variables, such as culture, gender, biological markers (i.e., blood sugar and blood pressure), and psychological factors exert on food intake.

In addition, loneliness and social isolation appear to affect the quality and quantity of sleep, which in turn have a negative impact on health (Azizi-Zeinalhajlou et al., 2022; Benson et al., 2021). Finally, it is associated with internal states such as abandonment, sadness, depression, social rejection, exclusion, and stressors, which can also promote inflammation (Brandt et al., 2022; Wolters et al., 2023) and increase the risk of developing cardiovascular diseases (Khandaker et al., 2020).

These findings confirm that loneliness is associated with negative health outcomes, health behaviours, and healthcare utilization (Hawkley, 2022; Holt-Lunstad, 2021).

On the contrary, the presence of meaningful relationships and a support network is a protective factor (Hutten et al., 2021). Studies that have examined the relationship between marital status and blood pressure report that interactions with family members and the spouse are associated with lower ambulatory blood pressure (Holt-Lunstad et al., 2008); conversely, negative marital relationship quality tends to increase blood pressure (Holt-Lunstad et al., 2008). In addition, satisfaction with a romantic relationship has a positive effect on health, inflammation, and HRV (Donoho et al., 2013, 2015). Finally, oxytocin appears to have a positive effect on cardiovascular reactivity, while loneliness reduces this benefit (Norman et al., 2011).

This underlines how important and crucial the quality of a relationship is. Indeed, the presence of relationships enables the development of social networks that facilitate access to many resources (e.g., economic) and opportunities (e.g., jobs) (Cohen, 2004), while socially isolated individuals have a smaller network from which to draw help (Steptoe et al., 2013).

In line with literature, our study highlights the role of variables such as gender and nationality on MetD mechanisms and their impact on health. In addition, the perception of loneliness is culturally driven and influenced by gender, which is an important factor in shaping social relationships (Heu et al., 2019; Maes et al., 2019).

Some major scientific institutions such as the American Heart Association are already asking doctors to ask their patients how often they socialize and whether they are satisfied with the amount of interaction they have with friends and relatives or with people who share the same interests. We are living in an age where loneliness is more prevalent, particularly among older people, and doctors should take this into account when assessing risks (European Society of Cardiology Council on Cardiovascular Nursing and Allied Professions, 2018).

Research examining this phenomenon finds that when people are isolated and lonely, they are more likely to suffer also from life-threatening cardiovascular events. Essentially, the impoverishment of social relationships seems to pave the way for comparable or even greater effects than traditional risk factors. This is a problem that should by no means be underestimated. The epicentre concerns the elderly: according to the latest data from the Istituto Superiore di Sanità, one in seven over-65s is at risk of social isolation.

Among the most likely biological mechanisms underlying the increased risk are the hypothalamic–pituitary–adrenal (HPA) axis and the activation of the sympathetic nervous system in response to stress. In the long term, stress can damage the immune system and the cardiovascular system. Another branch of research is concerned with proteomics, that is, the proteins that circulate in the blood (EuroHeartcare, 2018).

In terms of clinical implications, loneliness is a huge scourge of our time, and an issue that is receiving more and more attention on the international agenda and is also a particular challenge for public health. Loneliness is a kind of silent killer, and in this regard, initiatives to raise awareness among the population, clinicians, and institutions would be needed to improve knowledge about it. To address this complexity, health services are increasingly moving towards implementing multidisciplinary treatment protocols that adequately address the interrelationships between physical, psychological, and social components. Mental health professionals are therefore called upon to propose preventive measures aimed at improving awareness and knowledge of loneliness and its effects

among young people, adults, the elderly, institutions, the community, the medical environment, and the culture. In addition, the data reported in this review show a significant link between mind and body.

Limitations

Our review has some important limitations. First, only a small number of eligible articles were found, providing a limited amount of evidence. Furthermore, this search strategy did not allow us to analyse the individual effect of each of these components or to compare the different facets of loneliness. Most of the studies considered have samples older than 40/50 years, so the results of the review cannot be generalized to all age groups.

In addition, some important findings may have been overlooked in this review as only English language publications were included. Finally, few studies dealing with the circulatory and immune systems include an analysis of clinical-psychological variables such as loneliness. Therefore, this systematic review may in any case provide an incomplete picture of the relationship between loneliness, the immune system, and cardiovascular health.

Conclusions

Our systematic literature review confirms that loneliness is an important risk factor for cardiovascular health via direct and indirect pathways (e.g., the immune system).

From a clinical psychology perspective, it is therefore important to consider loneliness and social isolation as indicators of fragility, which may be related to cultural differences, an unhealthy environment, the unavailability of services, lack of opportunities to develop professional and social roles, disabilities, or a state of non-independence: these are multifactorial risk factors with a significant impact on physical and mental health, quality of life, and social costs.

It is therefore necessary to tackle loneliness and social isolation at the public health level.

Policymakers and health professionals should emphasize the need to develop interdisciplinary prevention and promotion strategies that include psychological and psychotherapeutic interventions. In addition, future research should be encouraged to investigate the relationship between loneliness and health and to develop and evaluate integrated interventions that could help to reduce the negative effects of loneliness. Moreover, future lines of research could focus on the assessment of loneliness and the subsequent identification of risk factors, the design and implementation of specific interventions for different groups of people (the elderly, young people, etc.) and the evaluation of the effectiveness of interventions.

AUTHOR CONTRIBUTIONS

Antonella Granieri: Conceptualization; writing – review and editing; supervision. **Maria Domenica Sauta:** Investigation; data curation; writing – original draft; writing – review and editing. **Giulia Cerutti:** Investigation; writing – original draft. **Alessandra De Luca:** Writing – review and editing; writing – original draft; investigation. **Claudia Ricco:** Writing – review and editing; investigation. **Carola Grimaldi:** Writing – original draft; investigation. **Marco Gonella:** Conceptualization; writing – review and editing. **Isabella Giulia Franzoi:** Conceptualization; investigation; methodology; writing – original draft; writing – review and editing; data curation; project administration.

CONFLICT OF INTEREST STATEMENT

We have no known interest to disclose.

DISCLOSURE

Mindful that our identities can influence our approach to science, the authors wish to provide the reader with information about our backgrounds. With respect to gender, when the manuscript was drafted, seven authors self-identified as women and one author as a man. With respect to race, all authors self-identified as white.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Antonella Granieri https://orcid.org/0000-0002-9823-9292
Maria Domenica Sauta https://orcid.org/0000-0003-3185-0633
Alessandra De Luca https://orcid.org/0009-0005-8389-682X
Carola Grimaldi https://orcid.org/0009-0000-8427-7792
Isabella Giulia Franzoi https://orcid.org/0000-0002-2455-330X

REFERENCES

Alcaraz, K., Eddens, K. S., Blasé, J. L., Diver, W. R., Patel, A. L., Teras, L. R., Stevens, V. L., Jacobs, E. J., & Gapstur, S. M. (2019). Social isolation and mortality in US black and white men and women. *American Journal of Epidemiology*, *188*(1), 102–109. https://doi.org/10.1093/aje/kwy231

Azizi-Zeinalhajlou, A., Mirghafourvand, M., Nadrian, H., Samei Sis, S., & Matlabi, H. (2022). The contribution of social isolation and loneliness to sleep disturbances among older adults: A systematic review. *Sleep and Biological Rhythms*, *20*(2), 153–163.

Barjaková, M., Garnero, A., & d'Hombres, B. (2023). Risk factors for loneliness: A literature review. *Social Science & Medicine*, *334*, 116163. https://doi.org/10.1016/j.socscimed.2023.116163

Becofsky, K. M., Shook, R. P., Sui, X., Wilcox, S., Lavie, C. J., & Blair, S. N. (2015). Influence of the source of social support and size of social network on all-cause mortality. *Mayo Clinic Proceedings*, *90*(7), 895–902. https://doi.org/10.1016/j.mayocp.2015.04.007

Bell, P., & Lawlor, B. (2023). Community Based Interventions for Loneliness. In D. V. Jeste, T. T. Nguyen, & N. J. Donovan (Eds.), *Loneliness: Science and Practice*. American Psychiatric Association Publishing.

Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., Chiuve, S. E., Cushman, M., Delling, F. N., Deo, R., de Ferranti, S. D., Ferguson, J. F., Fornage, M., Gillespie, C., Isasi, C. R., Jiménez, M. C., Jordan, L. C., Judd, S. E., Lackland, D., … American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. (2018). Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation*, *137*(12), e67–e492. https://doi.org/10.1161/CIR.0000000000000558

Benson, J. A., McSorley, V. E., Hawkley, L. C., & Lauderdale, D. S. (2021). Associations of loneliness and social isolation with actigraph and self-reported sleep quality in a national sample of older adults. *Sleep*, *44*(1), zsaa140.

Berman, M. G., Cárdenas-Iniguez, C., & Meidenbauer, K. L. (2021). An environmental neuroscience perspective on the benefits of nature. In M. van den Bosch & W. Bird (Eds.), *Nature and psychology: Biological, cognitive, developmental, and social pathways to well-being* (pp. 61–88). Springer. https://doi.org/10.1007/978-3-030-53536-7_4

Boyalla, V., Gallego-Colon, E., & Spartalis, M. (2023). Immunity and inflammation in cardiovascular disorders. *BMC Cardiovascular Disorders*, *23*(1), 148. https://doi.org/10.1186/s12872-023-03185-z

Brandt, L., Liu, S., Heim, C., & Heinz, A. (2022). The effects of social isolation stress and discrimination on mental health. *Translational Psychiatry*, *12*(1), 398.

Brouwers, C., Kupper, N., Pelle, A. J., Szabó, B. M., Westerhuis, B. L., & Denollet, J. (2014). Depressive symptoms in outpatients with heart failure: Importance of inflammatory biomarkers, disease severity and personality. *Psychology & Health*, *29*(5), 564–582. https://doi.org/10.1080/08870446.2013.869813

Brumariu, L. E., & Kerns, K. A. (2022). Parent–child attachment in early and middle childhood. In *The Wiley-Blackwell Handbook of Childhood Social Development* (pp. 425–442). Wiley.

Cazzato, V., Sacchetti, S., Shin, S., Makdani, A., Trotter, P. D., & McGlone, F. (2021). Affective touch topography and body image. *PLoS One*, *16*(11), e0243680.

Chen, H., Liu, F., Luo, J., Tu, Y., Huang, S., & Zhu, W. (2024). Association of living alone with clinical outcomes in patients with heart failure: A systematic review and meta-analysis. *Clinical Cardiology*, *47*(1), e24153. https://doi.org/10.1002/clc.24153

Christiansen, J., Lund, R., Qualter, P., Andersen, C. M., Pedersen, S. S., & Lasgaard, M. (2021). Loneliness, social isolation, and chronic disease outcomes. *Annals of Behavioral Medicine*, *55*(3), 203–215.

Cohen, S. (2004). Social relationships and health. *American Psychologist*, *59*(8), 676–684.

Das, K. V., Jones-Harrell, C., Fan, Y., Ramaswami, A., Orlove, B., & Botchwey, N. (2020). Understanding subjective well-being: perspectives from psychology and public health. *Public Health Reviews*, *41*, 1–32.

Delerue Matos, A., Barbosa, F., Cunha, C., Voss, G., & Correia, F. (2021). Social isolation, physical inactivity and inadequate diet among European middle-aged and older adults. *BMC Public Health*, *21*(1), 924.

d'Hombres, B., Barjaková, M., & Schnepf, S. V. (2021). Loneliness and social isolation: an unequally shared burden in Europe, Loneliness and Social Isolation: An Unequally Shared Burden in Europe.

DiJulio, B., Hamel, L., Muñana, C., & Brodie, M. (2018). *Loneliness and social isolation in the United States, the United Kingdom, and Japan: An international survey*. The Economist & Kaiser Family Foundation.

Djekic, D., Fagman, E., Angerås, O., Lappas, G., Torén, K., Bergström, G., & Rosengren, A. (2020). Social support and sub-clinical coronary artery disease in middle-aged men and women: Findings from the pilot of Swedish CArdioPulmonary bioImage study. *International Journal of Environmental Research and Public Health*, *17*(3), 778. https://doi.org/10.3390/ijerph17030778

Doane, L. D., & Adam, E. K. (2010). Loneliness and cortisol: Momentary, day-to-day, and trait associations. *Psychoneuroendocrinology*, *35*(3), 430–441.

Donoho, C. J., Crimmins, E. M., & Seeman, T. E. (2013). Marital quality, gender, and markers of inflammation in the MIDUS cohort. *Journal of Marriage and Family*, *75*(1), 127–141.

Donoho, C. J., Seeman, T. E., Sloan, R. P., & Crimmins, E. M. (2015). Marital status, marital quality, and heart rate variability in the MIDUS cohort. *Journal of Family Psychology*, *29*(2), 290–295.

Donovan, M., Mackey, C. S., Platt, G. N., Rounds, J., Brown, A. N., Trickey, D. J., Liu, Y., Jones, K. M., & Wang, Z. (2020). Social isolation alters behavior, the gut-immune-brain axis, and neurochemical circuits in male and female prairie voles. *Neurobiology of Stress*, *13*, 100278. https://doi.org/10.1016/j.ynstr.2020.100278

Erzen, E., & Çikrikci, Ö. (2018). The effect of loneliness on depression: A meta-analysis. *International Journal of Social Psychiatry*, *64*(5), 427–435.

European Society of Cardiology Council on Cardiovascular Nursing and Allied Professions. (2018). EuroHeartCare 2018: Tackling the complexity of cardiovascular care [Supplement]. *European Journal of Cardiovascular Nursing*, *17*(1_suppl), S1–S120. https://doi.org/10.1177/1474515118787764

Ford, J., Anderson, C., Gillespie, S., Giurgescu, C., Nolan, T., Nowak, A., & Williams, K. P. (2019). Social Integration and Quality of Social Relationships as Protective Factors for Inflammation in a Nationally Representative Sample of Black Women. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*, *96*(Suppl 1), 35–43. https://doi.org/10.1007/s11524-018-00337-x

Freak-Poli, R., Ryan, J., Neumann, J. T., Tonkin, A., Reid, C. M., Woods, R. L., Nelson, M., Stocks, N., Berk, M., McNeil, J. J., Britt, C., & Owen, A. J. (2021). Social isolation, social support and loneliness as predictors of cardiovascular disease incidence and mortality. *BMC Geriatrics*, *21*(1), 711. https://doi.org/10.1186/s12877-021-02602-2

Galanaki, E. (2013). The origins of solitude: Psychoanalytic perspectives. In *The handbook of solitude: Psychological perspectives on social isolation, social withdrawal, and being alone* (pp. 71–89). Wiley.

Gutkind, S., Gorfinkel, L. R., & Hasin, D. S. (2022). Prospective effects of loneliness on frequency of alcohol and marijuana use. *Addictive Behaviors*, *124*, 107115.

Hackett, R. A., Hamer, M., Endrighi, R., Brydon, L., & Steptoe, A. (2012). Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. *Psychoneuroendocrinology*, *37*(11), 1801–1809. https://doi.org/10.1016/j.psyneuen.2012.03.016

Hackett, R. A., Hudson, J. L., & Chilcot, J. (2020). Loneliness and type 2 diabetes incidence: Findings from the English Longitudinal Study of Ageing. *Diabetologia*, *63*(11), 2329–2338. https://doi.org/10.1007/s00125-020-05258-6

Hajek, A., Kretzler, B., & König, H. H. (2021). The association between obesity and social isolation as well as loneliness in the adult population: a systematic review. *Diabetes, Metabolic Syndrome and Obesity*, *14*, 2765–2773.

Hawkley, L. C. (2022). Loneliness and health. *Nature Reviews. Disease Primers*, *8*, 22. https://doi.org/10.1038/s41572-022-00355-9

Hawkley, L. C., Masi, C. M., Berry, J. D., & Cacioppo, J. T. (2006). Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychology and Aging*, *21*(1), 152–164. https://doi.org/10.1037/0882-7974.21.1.152

Heffner, K. L., Waring, M. E., Roberts, M. B., Eaton, C. B., & Gramling, R. (2011). Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults. *Social Science & Medicine (1982)*, *72*(9), 1482–1488. https://doi.org/10.1016/j.socscimed.2011.03.016

Henriksen, R. E., Nilsen, R. M., & Strandberg, R. B. (2019). Loneliness as a risk factor for metabolic syndrome: Results from the HUNT study. *Journal of Epidemiology & Community Health*, *73*(11), 941–946. https://doi.org/10.1136/jech-2019-212335

Heu, L. C., van Zomeren, M., & Hansen, N. (2019). Lonely alone or lonely together? A cultural-psychological examination of in-dividualism–collectivism and loneliness in five European countries. *Personality and Social Psychology Bulletin*, *45*(5), 780–793.

Hodgson, S., Watts, I., Fraser, S., Roderick, P., & Dambha-Miller, H. (2020). Loneliness, social isolation, cardiovascular disease and mortality: A synthesis of the literature and conceptual framework. *Journal of the Royal Society of Medicine*, *113*, 185–192.

Holt-Lunstad, J. (2021). Loneliness and social isolation as risk factors: The power of social connection in prevention. *American Journal of Lifestyle Medicine*, *15*(5), 567–573. https://doi.org/10.1177/15598276211009454

Holt-Lunstad, J., Birmingham, W., & Jones, B. Q. (2008). Is there something unique about marriage? The relative impact of marital status, relationship quality, and network social support on ambulatory blood pressure and mental health.

Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine, *35*(2), 239–244. https://doi.org/10.1007/s12160-008-9018-y

Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T., & Stephenson, D. (2015). Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspectives on Psychological Science*, *10*(2), 227–237. https://doi.org/10.1177/1745691614568352

Holt-Lunstad, J., & Steptoe, A. (2022). Social isolation: An underappreciated determinant of physical health. *Current Opinion in Psychology*, *43*, 232–237.

Horigian, V. E., Schmidt, R. D., & Feaster, D. J. (2021). Loneliness, mental health, and substance use among US young adults during COVID-19. *Journal of Psychoactive Drugs*, *53*(1), 1–9.

Hutten, E., Jongen, E. M., Vos, A. E., van den Hout, A. J., & van Lankveld, J. J. (2021). Loneliness and mental health: The mediating effect of perceived social support. *International Journal of Environmental Research and Public Health*, *18*(22), 11963.

Jaremka, L. M., Fagundes, C. P., Peng, J., Bennett, J. M., Glaser, R., Malarkey, W. B., & Kiecolt-Glaser, J. K. (2013). Loneliness promotes inflammation during acute stress. *Psychological Science*, *24*(7), 1089–1097. https://doi.org/10.1177/0956797612464059

Kapoulea, E. A., Ready, R. E., & Ginn, J. C. (2023). Loneliness and risk for cardiovascular disease in the United States and Japan: The effects of nationality, collectivism, and gender. *Social Science & Medicine*, *337*, 116299. https://doi.org/10.1016/j.socscimed.2023.116299. Epub 2023 Oct 9. PMID: 37837950.

Khandaker, G. M., Zuber, V., Rees, J. M. B., Carvalho, L., Mason, A. M., Foley, C. N., & Burgess, S. (2020). Shared mechanisms between coronary heart disease and depression: Findings from a large UK general population-based cohort. *Molecular Psychiatry*, *25*(7), 1477–1486. https://doi.org/10.1038/s41380-019-0395-3

Kim, D. A., Benjamin, E. J., Fowler, J. H., & Christakis, N. A. (2016). Social connectedness is associated with fibrinogen level in a human social network. *Proceedings. Biological sciences*, *283*(1837), 20160958. https://doi.org/10.1098/rspb.2016.0958

Klein, M. (1959). *Sul senso di solitudine, tr. it. in "Il nostro mondo adulto"*. Martinelli. 1974.

Köteles, F. (2021). *Body sensations*. Springer International Publishing.

Kraav, S. L., Awoyemi, O., Junttila, N., Vornanen, R., Kauhanen, J., Toikko, T., Lehto, S. M., Hantunen, S., & Tolmunen, T. (2021). The effects of loneliness and social isolation on all-cause, injury, cancer, and CVD mortality in a cohort of middle-aged Finnish men. A prospective study. *Aging & Mental Health*, *25*(12), 2219–2228. https://doi.org/10.1080/13607863.2020.1830945

Kriakous, S. A., Elliott, K. A., Lamers, C., & Owen, R. (2021). The Effectiveness of Mindfulness-Based Stress Reduction on the Psychological Functioning of Healthcare Professionals: a Systematic Review. *Mindfulness*, *12*, 1–28. https://doi.org/10.1007/s12671-020-01500-9

Li, H., Li, S., Yang, H., Zhang, Y., Xu, F., Cao, Z., Ma, Y., Hou, Y., Borne, Y., & Wang, Y. (2022). Association of comprehensive mental health with incident cardiovascular disease: A prospective cohort study. *Journal of Affective Disorders*, *298*(Pt A), 388–395. https://doi.org/10.1016/j.jad.2021.11.008

Li, L. Z., & Wang, S. (2020). Prevalence and predictors of general psychiatric disorders and loneliness during COVID-19 in the United Kingdom. *Psychiatry Research*, *291*, 113267. https://doi.org/10.1016/j.psychres.2020.113267

Liang, Y. Y., Zhou, M., He, Y., Zhang, W., Wu, Q., Luo, T., Zhang, J., Jia, F., Qi, L., Ai, S., & Zhang, J. (2024). Observational and genetic evidence disagree on the association between loneliness and risk of multiple diseases. *Nature Human Behaviour*, *8*(11), 2209–2221. https://doi.org/10.1038/s41562-024-01970-0

Long, M., Verbeke, W., Ein-Dor, T., & Vrtička, P. (2020). A functional neuro-anatomical model of human attachment (NAMA): Insights from first-and second-person social neuroscience. *Cortex*, *126*, 281–321.

Maes, M., Qualter, P., Vanhalst, J., Van den Noortgate, W., & Goossens, L. (2019). Gender differences in loneliness across the lifespan: A meta–analysis. *European Journal of Personality*, *33*(6), 642–654.

McMahon, G., Howard, S., Manunta, E., Griffin, S., Bradshaw, D., Nightingale, A., & Muldoon, O. T. (2024). Social group membership and biomarkers of health. *Journal of Applied Social Psychology*, *54*(7), 405–415. https://doi.org/10.1111/jasp.13048

Mental Health Foundation. (2020). *Almost a quarter of adults living under lockdown in the UK have felt loneliness*. Mental Health Foundation. https://www.cam.ac.uk/research/news/almost-a-quarter-of-adults-living-under-lockdown-in-the-uk-have-experienced-loneliness

Mezuk, B., Diez Roux, A. V., & Seeman, T. (2010). Evaluating the buffering vs. direct effects hypotheses of emotional social support on inflammatory markers: the multi-ethnic study of atherosclerosis. *Brain, Behavior, and Immunity*, *24*(8), 1294–1300. https://doi.org/10.1016/j.bbi.2010.06.006

Moola, S., Munn, Z., Tufanaru, C., Aromataris, E., Sears, K., Sfetcu, R., Currie, M., Qureshi, R., Mattis, P., Lisy, K., & Mu, P.-F. (2020). Critical appraisal checklists for analytical cross-sectional studies, qualitative research, and randomized controlled trials. In E. Aromataris & Z. Munn (Eds.), *JBI Manual for Evidence Synthesis*. Joanna Briggs Institute. https://synthesismanual.jbi.global

Nagayoshi, M., Everson-Rose, S. A., Iso, H., Mosley, T. H., Jr., Rose, K. M., & Lutsey, P. L. (2014). Social network, social support, and risk of incident stroke: Atherosclerosis Risk in Communities study. *Stroke*, *45*(10), 2868–2873. https://doi.org/10.1161/STROKEAHA.114.005815

Norman, G. J., Cacioppo, J. T., Morris, J. S., Malarkey, W. B., Berntson, G. G., & Devries, A. C. (2011). Oxytocin increases autonomic cardiac control: moderation by loneliness. *Biological Psychology*, *86*(3), 174–180. https://doi.org/10.1016/j.biopsycho.2010.11.006

O'Luanaigh, C., O'Connell, H., Chin, A. V., Hamilton, F., Coen, R., Walsh, C., Walsh, J. B., Coakley, D., Molloy, A., Scott, J., Cunningham, C. J., & Lawlor, B. A. (2012). Loneliness and vascular biomarkers: the Dublin Healthy Ageing Study. *International Journal of Geriatric Psychiatry*, *27*(1), 83–88. https://doi.org/10.1002/gps.2695

Olvera Lopez, E., Ballard, B. D., & Jan, A. (2023). Cardiovascular disease. In *StatPearls*. StatPearls Publishing.

Otten, D., Ernst, M., Werner, A. M., Tibubos, A. N., Reiner, I., Brähler, E., Wiltink, J., Michal, M., Nagler, M., Wild, P. S., Münzel, T., König, J., Lackner, K. J., Peiffer, N., & Beutel, M. E. (2023). Depressive symptoms predict the incidence of common chronic diseases in women and men in a representative community sample. *Psychological Medicine*, *53*(9), 4172–4180. https://doi.org/10.1017/S0033291722000861

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*, *372*, n71. https://doi.org/10.1136/bmj.n71

Pavela, G., Kim, Y. I., & Salvy, S. J. (2018). Additive effects of obesity and loneliness on C-reactive protein. *PLoS One*, *13*(11), e0206092. https://doi.org/10.1371/journal.pone.0206092

Pollard, E. L., & Lee, P. D. (2003). Child well-being: A systematic review of the literature. *Social Indicators Research*, *61*(1), 59–78. https://doi.org/10.1023/A:1021284215801

Pourriyahi, H., Yazdanpanah, N., Saghazadeh, A., & Rezaei, N. (2021). Loneliness: An Immunometabolic syndrome. *International Journal of Environmental Research and Public Health*, *18*(22), 12162. https://doi.org/10.3390/ijerph182212162

Putra, I. G. N. E., Daly, M., Sutin, A., Steptoe, A., & Robinson, E. (2023). Psychological pathways explaining the prospective association between obesity and physiological dysregulation. *Health Psychology*, *42*(7), 472–484. https://doi.org/10.1037/hea0001284

Radloff, L. S. (1977). The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Richard, A., Rohrmann, S., Vandeleur, C. L., Schmid, M., Barth, J., & Eichholzer, M. (2017). Loneliness is adversely associated with physical and mental health and lifestyle factors: Results from a Swiss national survey. *PLoS One*, *12*(7), e0181442.

Roddick, C. M., & Chen, F. S. (2021). Effects of Chronic and State Loneliness on Heart Rate Variability in Women. *Annals of Behavioral Medicine*, *55*(6), 460–475. https://doi.org/10.1093/abm/kaaa065

Ross, E. J., Jimenez, D. E., Ghanooni, D., Mendez, A., Hirshfield, S., Horvath, K. J., DeVries, B., Dilworth, S. E., Carrico, A. W., & Martinez, C. A. (2024). Loneliness, Methamphetamine Use, and Cardiovascular Risk Factors Among Sexual Minority Men in the COVID-19 Era. *International Journal of Behavioral Medicine*, *32*(2), 267–275. https://doi.org/10.1007/s12529-024-10288-0

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *30*(4), 377–385. https://doi.org/10.1037/a0022826

Shen, C., Zhang, R., Yu, J., Sahakian, B. J., Cheng, W., & Feng, J. (2025). Plasma proteomic signatures of social isolation and loneliness associated with morbidity and mortality. *Nature Human Behaviour*, *9*(3), 569–583. https://doi.org/10.1038/s41562-024-02078-1

Shiovitz-Ezra, S., & Parag, O. (2019). Does loneliness 'get under the skin'? Associations of loneliness with subsequent change in inflammatory and metabolic markers. *Aging and Mental Health*, *23*(10), 1358–1366. https://doi.org/10.1080/13607863.2018.1488942

Singh, M., Nag, A., Gupta, L., Thomas, J., Ravichandran, R., & Panjiyar, B. K. (2023). Impact of Social Support on Cardiovascular Risk Prediction Models: A Systematic Review. *Cureus*, *15*(9), e45836. https://doi.org/10.7759/cureus.45836

Speroni, J., Fanniff, A. M., Edgemon, J. M., Martini, V., & Haas, A. L. (2023). Alcohol mixed with energy drinks and aggressive behaviors in adolescents and young adults: A systematic review. *Clinical Psychology Review*, *104*, 102319. https://doi.org/10.1016/j.cpr.2023.102319

Steptoe, A., Shankar, A., Demakakos, P., & Wardle, J. (2013). Social isolation, loneliness, and all-cause mortality in older men and women. *Proceedings of the National Academy of Sciences*, *110*(15), 5797–5801.

Stokes, J., & Carr, D. (2020). Marital Effects in Later Life: Dyadic Approaches and Gender Differences. *Innovation in Aging*, *4*(Supplement_1), 604–605.

Stringhini, S., Zaninotto, P., Kumari, M., Kivimäki, M., Lassale, C., & Batty, G. D. (2018). Socio-economic trajectories and cardiovascular disease mortality in older people: the English Longitudinal Study of Ageing. *International Journal of Epidemiology*, *47*(1), 36–46. https://doi.org/10.1093/ije/dyx106

Teshale, A. B., Htun, H. L., Hu, J., Dalli, L. L., Lim, M. H., Neves, B. B., & Freak-Poli, R. (2023). The relationship between social isolation, social support, and loneliness with cardiovascular disease and shared risk factors: A narrative review. *Archives of Gerontology and Geriatrics*, *111*, 105008.

Valtorta, N. K., Kanaan, M., Gilbody, S., Ronzi, S., & Hanratty, B. (2016). Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart*, *102*(13), 1009–1016.

Vasan, S., Lim, M. H., Eikelis, N., & Lambert, E. (2024). Investigating the relationship between early cardiovascular disease markers and loneliness in young adults. *Scientific Reports*, *14*(1), 14221.

Vingeliene, S., Hiyoshi, A., Lentjes, M., Fall, K., & Montgomery, S. (2019). Longitudinal analysis of loneliness and inflammation at older ages: English longitudinal study of ageing. *Psychoneuroendocrinology*, *110*, 104421. https://doi.org/10.1016/j.psyne uen.2019.104421

WHO. (2024). Global health estimates: Leading causes of death. 2000-2021. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

Winnicott, D. W. (1958). The Capacity to be Alone. *International Journal of Psycho-Analysis*, *39*, 416–420. Tr. it. in "Sviluppo affettivo e ambiente" Armando Editore, Roma, 1970.

Wolters, N. E., Mobach, L., Wuthrich, V. M., Vonk, P., der Van Heijde, C. M., Wiers, R. W., & Klein, A. M. (2023). Emotional and social loneliness and their unique links with social isolation, depression and anxiety. *Journal of Affective Disorders*, *329*, 207–217.

Woodhouse, S. S., Scott, J. R., Hepworth, A. D., & Cassidy, J. (2020). Secure base provision: A new approach to examining links between maternal caregiving and infant attachment. *Child Development*, *91*(1), e249–e265.

Wright, S. (2023). "Loneliness and the void": Exploring different types of aloneness and the lack of benign internal objects. *Attachment: New Directions in Psychotherapy and Relational Psychoanalysis*, *17*, 27–42. https://doi.org/10.33212/att.v17n1.2023.27

Xia, N., & Li, H. (2018). Loneliness, social isolation, and cardiovascular health. *Antioxidants & Redox Signaling*, *28*(9), 837–851. https://doi.org/10.1089/ars.2017.7312

Yang, J., Yockey, R. A., Chu, Y., & Lee, J. G. L. (2022). The influence of loneliness on the smoking and physical activity of community-dwelling older adults: Results from the health and retirement study. *American Journal of Health Promotion*, *36*(6), 959–966. https://doi.org/10.1177/08901171221081136

Yang, Y. C., McClintock, M. K., Kozloski, M., & Li, T. (2013). Social isolation and adult mortality: The role of chronic inflammation and sex differences. *Journal of Health and Social Behavior*, *54*(2), 183–203. https://doi.org/10.1177/0022146513485244

Zheng, X., Zhang, K., & Ma, J. (2023). The longitudinal relationship between Frailty, Loneliness and Cardiovascular Disease: a prospective cohort study. *The Journal of Nutrition, Health and Aging*, *27*(12), 1212–1218.

Zhou, J., Tang, R., Wang, X., Li, X., Heianza, Y., & Qi, L. (2024). Improvement of social isolation and loneliness and excess mortality risk in people with obesity. *JAMA Network Open*, *7*(1), e2352824.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.