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The association between loneliness, social isolation and inflammation: A systematic review and meta-analysis

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ABSTRACT

The review synthesised evidence examining the association between a. loneliness with inflammation and b. social isolation with inflammation in adults aged 16 or older from the general population. From an initial 7,400 articles we identified 14 papers that examined loneliness, and 16 that examined social isolation. Qualitative syntheses indicated mixed results, variable study quality, and methodological heterogeneity. Most studies provided associations for C-reactive protein CRP, fibrinogen and Interleukin-6 IL-6, and these results were synthesised using random-effects meta-analyses. There was no association between loneliness with CRP or fibrinogen, but there was a significant association between loneliness and IL-6 for most-adjusted but not least-adjusted analyses. There was also a significant least-adjusted association between social isolation with CRP and fibrinogen, which remained significant for fibrinogen in most-adjusted analyses. There was no association between social isolation with IL-6. Sensitivity analyses indicated that methodological heterogeneity impacted on results. Results indicate that social isolation and loneliness could be linked with systemic inflammation, but more robust methodology is needed to confirm these associations and unpack mechanisms.

1. Introduction

Researchers define loneliness as the perception of feeling isolated and social isolation as the objective state of being isolated from people (Rook, 1984). More specifically, loneliness represents the discrepancy between the desired and actual quality and quantity of social relationships that a person has (Perlman and Peplau, 1981). Whereas, social isolation represents a lack of meaningful contact with a person's social network or community (Victor et al., 2000).

An increasing body of evidence indicates both loneliness and social isolation are risk factors for worsened health outcomes such as heart disease, stroke, dementia and even mortality (Holt-Lunstad et al., 2015; Kuiper et al., 2015; Leigh-Hunt et al., 2017; Valtorta et al., 2016). Researchers have proposed that these poorer health outcomes could be the result of loneliness and social isolation having a direct physiological impact on the body (Cacioppo et al., 2002, 2014, 2015; Hawkley and Cacioppo, 2003; Karelina and DeVries, 2011). Therefore, there is an interest in better understanding how loneliness and social isolation impact on people physiologically. One physiological response to loneliness and social isolation that could also lead to worsened health is increased inflammation (Hawkley and Cacioppo, 2003; Kiecolt-Glaser et al., 2010).

Inflammation represents a biological response to infection or injury whereby the body increases production of various chemicals that help to fight off infection (Serhan et al., 2010). Alongside biological threats, research shows that an enhanced inflammatory response may also occur in reaction to social stressors and social threats (Audet et al., 2014; Eisenberger et al., 2017; Hänsel et al., 2010; Hennessy et al., 2014; Leschak and Eisenberger, 2019). Scholars propose that because humans have evolved to be a socially-oriented species, that contact with society is necessary to provide biological, psychological and social regulation (Cruces et al., 2014). More specifically, perceived social isolation (loneliness) and objective social isolation are proposed to have a biological impact because they act as social stressors and activate the bodies stress response (Eisenberger, 2012; Hawkley and Cacioppo, 2003). Previous work shows that activation of the stress response (sympatheic nervous system and hypothalamic-pituitary-adrenocortical axis), has a direct effect on the bodies inflammatory response

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(Eisenberger et al., 2017). Furthermore, it is proposed that loneliness and social isolation could modify the bodies response to social and biological stressors, such that when a social or biological challenge occurs that those people who are lonely or socially isolated have an enhanced inflammatory response (Eisenberger et al., 2017). Some researchers also propose an evolutionary explanation for the activation of the inflammatory system in response to loneliness and social isolation (Leschak and Eisenberger, 2019). This is because when socially isolated a person would have been more likely to be attacked or wounded than when they were around others who could protect them. Therefore, the activation of the inflammatory response when one perceives social isolation (loneliness) or is socially isolated could confer evolutionary advantage as people would be prepared to respond biologically to this increased threat (Eisenberger et al., 2017; Leschak and Eisenberger, 2019). Interestingly, a recent synthesis showed that increasing social integration and higher levels of support were linked with lowered inflammation (Uchino et al., 2018). Therefore, one could hypothesise that indicators of worsened social integration might be linked with increased inflammation.

Previous narrative syntheses suggest that both loneliness and social isolation are associated with increased expression of inflammatory markers (Eisenberger et al., 2017; Leschak and Eisenberger, 2019). There is a particular interest in markers of systemic inflammation such as cytokines, chemokines and acute-phase proteins as these inflammatory markers have been linked with many of the same health outcomes as loneliness and social isolation such as cardiovascular disease, dementia and mortality (Kuo et al., 2005; Lai et al., 2017; Li et al., 2017; Mehra et al., 2005; Shin et al., 2002).

Despite previous narrative syntheses suggesting that both loneliness and social isolation are associated with increased expression of systemic inflammatory markers (Eisenberger et al., 2017; Leschak and Eisenberger, 2019) there is no systematic synthesis that has ever investigated these associations. Thus, the main aim of this systematic review is to synthesise those studies that have examined the association of a.) loneliness with cytokines, chemokines and/or acute-phase proteins or b.) social isolation with cytokines, chemokines and/or acute-phase proteins in adults from the general population aged 16 or older. The secondary aim of the review is to examine sources of potential heterogeneity between studies to determine robustness of associations.

2. Methods

2.1. Search strategy

A systematic review was undertaken by KS and SG between September 2018 and March 2019, with an update search for newly published articles undertaken in July 2019. No restrictions regarding publication date or language were placed on the search, though only English papers were reviewed.

The search was conducted across five major databases: PubMed (United States National Library of Medicine, Bethesda, MD, USA), ProQuest (ProQuest, Ann Arbor, MI, USA), EBSCOHost (EBSCO Industries, Ipswich, MA, USA), Scopus (Elsevier, Amsterdam, Netherlands), and ISI Web of Science (Thomson Reuters, New York, NY, USA).

In addition, hand searches were undertaken in the bibliographies of narrative reviews identified during the search and in the abstract booklets of relevant psychoneuroimmunology and psychosomatic medicine conferences.

The study protocol was registered on PROSPERO prior to the study been undertaken: [ID: CRD42017069070].

2.2. Study selection

The following **P**opulation **I**ntervention **C**omparison **O**utcome (PICO) criteria were applied to the search: Studies that examine the association between loneliness (intervention/comparison) and inflammation (outcome) or social isolation (intervention/comparison) and inflammation (outcome) in adults aged 16 or older in the general population (population). Search terms relating to the major topics of loneliness OR social isolation AND inflammation were combined using the Boolean operators “or” plus “and” (see Appendix I).

Studies eligible for inclusion were required to examine loneliness using either a loneliness questionnaire or direct single-item question on how lonely a person felt. To be included, studies had to examine the relationship between increasing levels of loneliness with inflammation or compare lonely people with a reference group of people who were not lonely.

As there is also a lack of consensus in how researchers measure social isolation (Nicholson Jr, 2009) we identified studies that examined an absence of ties, social relationships or lack of contact with others as in Valtorta et al. (2016). To be included, studies were required to provide a measure which indicated a lack of social ties, lack of social relationships and/or lack of contacts or compare socially isolated people to a reference group of people who were not socially isolated.

For our outcome measure studies needed to examine at least one of the following indicators of inflammation: circulating (measured in blood) levels of cytokines, chemokines or acute-phase proteins. We limited our inflammatory markers to these indicators as they are indicators of systemic inflammation commonly measured in general population and community studies.

Exclusion criteria for studies included those studies conducted only in people with a chronic physical and/or psychiatric condition or illness, as this could influence levels of inflammation. We also excluded any experimental studies that had manipulated variables other than loneliness or isolation (though if the studies had baseline data pertaining to the relationship between loneliness and/or social isolation with inflammation they were included).

Two authors (KS and SG) independently screened all potentially eligible studies through a 3-stage process where articles were screened based on titles, followed by abstracts and finally full-texts (see Fig. 1). Where disagreements occurred these were resolved through discussion, or if necessary a third author (NR resolved discrepancies regarding inflammation and CV resolved discrepancies regarding loneliness or social isolation).

2.3. Data extraction and quality assessment

Data extraction and quality assessment were performed by one author (KS), with a second author (PK) independently extracting data and assessing quality for a third of the included studies. Any disagreements were resolved through consensus.

We extracted the following characteristics from each study: Authors and date of publication; study characteristics (study name, country and number of participants); participant characteristics (age, sex and ethnicity); loneliness measurement (measure used, scoring used and proportion lonely); inflammation measurement (inflammatory markers measures, assay method and venesection protocol); statistical analysis (type of statistical test and confounders controlled for) and measures of association (unadjusted/least adjusted and/or most adjusted).

Quality assessment was performed using a modified version of the Newcastle-Ottawa Scale (see Appendix II). The following characteristics of each study were assessed: Participants being representative of the general population or community, all participants being drawn from the same population, the predictor (loneliness or social isolation) being measured with a validated scale, the study controlled for all of the following important confounders (sociodemographics, chronic conditions, cardiometabolic abnormalities and lifestyle), the study design or analysis taking account of variables that could affect levels of inflammation (examples include excluding people with very high inflammation indicative of acute inflammation (e.g., > 10 mg/dL), blood samples being taken at the same time of day, people being asked to fast/

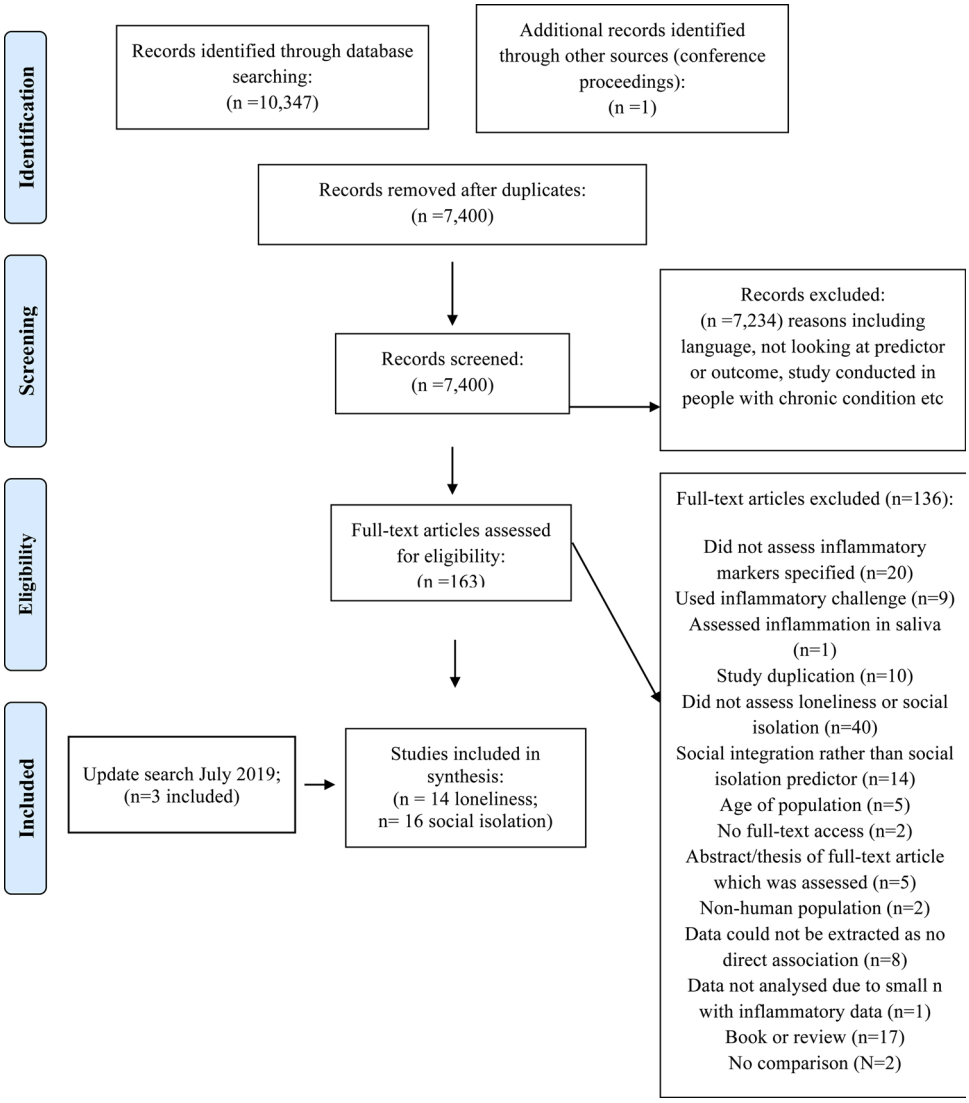

Fig. 1. PRISMA flow diagram study selection.

not drink caffeine/not exercise prior to bloods being taken, and/or people being excluded based on having an acute illness or taking medications that influence inflammation) and inflammation being assessed with a standardised inflammation protocol (i.e., measuring inflammation with a validated and consistent assay). Studies were awarded one star for each of the criteria that they met, and higher study quality was indicated by more stars being awarded. We used the following cut-points to identify study quality as was done in Smith et al. (2018): High quality (5 or 6 stars), moderate quality (3 or 4 stars) and low quality (0–2 stars).

2.4. Quantitative synthesis: meta-analyses

Quantitative results were synthesised using random-effects meta-analyses, which provide more conservative estimates when heterogeneity is a potential issue.

Data for the association of loneliness and social isolation with each inflammatory marker were synthesised separately. In order to be synthesised quantitatively a minimum of two studies per inflammatory marker were required. Where only one study examined an inflammatory marker this study was assessed qualitatively but not quantitatively. We also stratified our synthesis by the number of confounders adjusted for: least-adjusted (adjusted for a maximum of two confounders) and most-adjusted (model where the highest number of confounders were controlled for). We opted to include both models to account for any overestimation of effect sizes that could occur from only synthesising least-adjusted estimates.

For the least-adjusted analysis the preferred data for synthesis were means for different groups, or frequencies of people with high inflammation across different groups. The rationale for this was that some studies had least-adjusted analyses that were adjusting for more than two confounders and some studies had different reference groups. Where studies compared more than two groups, the data for the most lonely or most isolated group was compared with the mean level of inflammation across all other non-lonely or non-isolated groups. If means or frequencies were not available we preferred effect sizes that could be directly entered into the meta-analysis software such as correlations or odds ratios.

Where studies only provided the results from linear regression analyses with β, these were transformed into a correlation coefficient using the formula of Peterson and Brown (2005): $r = \beta + 0.5\lambda$ as the software used for the synthesis does not allow researchers to directly input β values.

Where studies provided stratified estimates (by age or sex), these were firstly synthesised into a single effect size before being entered into the meta-analysis.

Effect sizes were calculated as correlation coefficients (r) and 95 % confidence intervals (CI's). Alongside the main effect size, we also

Table 1
Studies examining the association between loneliness with inflammation.

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex AgeFemale (F)	LonelinessMeasure.Loneliness score.	InflammationMeasure Markers	 Assay methodBlood draw protocol	Statistical Analysis	Confounders adjusted	Results Least adjusted *(adjusted for maximum of 2 confounders)*	 Most adjusted
Cho et al., 2015.	Coronary Artery Risk Development Study in Young Adults USA N = 2692	Mean 40.3, SD 3.6 F = 56.1 %	Subjective social isolation score (4 loneliness items, 4 emotional support items, 4 negative support items)	CRP IL-6	CRP: Immuno-photometric assay IL-6: ELISA Not stated whether fasting sample	Pearson's R	N/A	CRP: r = .063, p = .0006 IL-6: r = .075, p < .0001	–
Hackett et al., 2012	Whitehall II: Civil servants UK N = 524	Age 53–76 (mean 61.18, SD 5.8) F: 45.99 %	R-UCLA 20-item Men mean 35.00, SD 11.4 Female mean 34.2, SD 9.7	IL-1Ra MCP-1 IL-6	IL-1Ra and MCP-1: Flow cytometry IL-6: ELISA Prohibited from drinking caffeinated drinks or vigorous exercise 2 hours prior to testing. Prohibited from taking anti-inflammatory medication or anti-histamine medication 7 days prior to study. Excluded/ rescheduled if reported acute illness.	Multiple linear regression (log transformed IL-1RA and MCP-1)	Age, grade of employment, BMI, and smoking status	–	IL-1Ra: B 0.006 (0.004-0.016), p = .21 IL-6: B 0.007 (0.006-0.020), p = .28 MCP-1 B 0.008 (0.004-0.012), p < .001
Hasselmo et al., 2018	Recent divorcees USA N = 46 (3 people excluded due to high CRP)	Mean age 44.08, SD 11.6 F: 69.4 %	3-item UCLA loneliness scale	IL-6 hsCRP	IL-6: ELISA hsCRP: diagnostic assay All samples collected between 8am to 12 pm. Participants screened out if taken anti-inflammatory medications, had a history of auto-immune diseases or drank excessive caffeine.	Correlation	–	CRP: r = .21, ns IL-6: r = .23, ns	
Lutengorf et al., 2004	65 + Rural Health Study (part of Established Populations for Epidemiologic Studies of the Elderly) USA N = 557	Aged 65–89 (mean 71.30, SD 4.88) F: 61 %	4-item version of UCLA loneliness scale	IL-6	ELISA Blood taken between 8am to 1 pm. Not stated whether fasting sample or not.	Pearson's correlation	–	*r*= -.03 (554), ns	–
Matthews et al., 2019	Environmental Risk Longitudinal Twin Study UK N = 2,232	Aged 18	4-item version of UCLA loneliness scale Mean 1.57, SD 1.94	CRP	High sensitivity assay Collected via blood spots (no further information available)	Linear regression (log transformed CRP)	–	β= -0.04 (95 % CI -0.08, -0.01), p = .134 *Nb: Adjusted for gender and socioeconomic status*	
					ELISA			–	

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Table 1 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex AgeFemale (F)	LonelinessMeasure.Loneliness score.	InflammationMeasure Markers	 Assay methodBlood draw protocol	Statistical Analysis	Confounders adjusted	Results Least adjusted *(adjusted for maximum of 2 confounders)*	 Most adjusted
McDade et al., 2006	Chicago Health, Aging and Social Relations Study USA N = 188	Aged 52-80 F: 55.3 %	UCLA loneliness scale Mean 35.7, SD 9.4	CRP *(removed people with > 8.6 mg/L)*		Multiple linear regression (log transformed CRP)	Age, race/ethnicity, education		B = 0.0017 (SE 0.0040), p = 0.67
Mezuk et al., 2016	Multi-Ethnic Study of Athero-sclerosis USA N = 441	Aged 45–84 (mean 63.4, SD 8.9) F: 53.7 %	3-item UCLA loneliness scale (score 3–9) highly lonely 6-9 17.2% highly lonely	hsCRP Fibrinogen	Nephelometry Fasting blood sample	A.) F-tests B.) Linear regression. Log adjusted inflammation C.) Logistic regression (high CRP > 3 mg/L outcome) *Nb: Analyses stratified for loneliness severity in paper*	A.) N/A B, C.) Age, sex, race/ethnicity, smoking status, drinking status, education, BMI, prevalent hypertension or diabetes, recent infection, and current use of anti-inflammatory medication	A.) **CRP** Not lonely: M 0.55 (SD 1.05) Moderate loneliness: M 0.43 (SD 1.07) High loneliness: M 0.55 (SD 0.94) p = .578 **Fibrinogen** Not lonely: M 5.92 (SD 0.20) Moderate loneliness: M 5.94 (SD 0.20) High loneliness: M 5.88 (SD 0.22) p = .089	B.) **CRP** β=-0.03(0.03), p = .269 **Fibrinogen** β=-0.01(0.01), p = .043 C.) **CRP** OR 0.84 (0.67–1.06)
Moller and Kristensen, 1991	Community study (Copen-hagan) Denmark N = 438	51 years old F: 0%	Single-item question whether in the past month had felt lonely (4 possible responses)	Fibrinogen	Gavimetric method Blood draw protocol not specified	Multiple linear regression	Abdominal index, problem index, self-rated health	p = .12	β = 0.38, p = .43
Nersesian et al., 2018	Midlife in the US study. USA. N = 927	Age 35–64 (mean 51.90, SD 7.5). F = 42.5 %	Single item question "During the past week I felt lonely…" Lonely: a little of the time to most/all of the time. 29 % lonely.	IL-6 Fibrinogen CRP	IL-6: ELISA Fibrinogen: Nephlometry CRP: immune-nephelometric assay Fasting blood sample on day 2 of study	IL-6 and CRP log-transformed A.) Students t-test B.) Multiple regression	B.) Age, sex, ethnicity, education, marital status, perceived stress, social integration, social support, psychological wellbeing, smoking status, chronic conditions, blood pressure, BMI.	A.) **IL-6** Lonely: M 3.49 pg/ml, SD 3.46 Not lonely: M 2.54 pg/ml, SD 2.39 p < .001 **Fibrinogen** Lonely: M 360.35 mg/dl, SD 90.41 Not lonely: M 336.83 mg/dl, SD 80.91 p < .001 **CRP** Lonely: M 3.68 mg/dl, SD 4.76 Not lonely: M 2.63 mg/dl, SD 3.71	B.) IL-6: b = 0.07 (0.01-0.12), p = .014 Fibrinogen b = 18.24 (4.26–32.21), p = .01 CRP b = 0.08 (0.01-0.16), p = .035

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Table 1 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex AgeFemale (F)	LonelinessMeasure.Loneliness score.	InflammationMeasure Markers	 Assay methodBlood draw protocol	Statistical Analysis	Confounders adjusted	Results Least adjusted *(adjusted for maximum of 2 confounders)*	 Most adjusted
								p < .001 B.) **IL-6** b = 0.1 (0.06-0.14), p < .001 **Fibrinogen** b = 19.69 (7.10–32.29), p = 0.02 **CRP** b = 0.10 (0.03-0.18), p = .009	
O'Luanaigh et al., 2012	Dublin Healthy Ageing Study Ireland N = 466	Mean 75.45, SD 6.06 F: 55.4 %	Single item question "do you feel lonely"? Identified as lonely if responded sometimes or often. 15.7 % lonely	CRP	Immuno-phelometry Non-fasting blood sample	ANOVA	–	Lonely: M 7.42 mg/l (SD 11.0) Non-lonely: M 7.29 mg/l (SD 14.54) p = ns	–
Pavela et al., 2018	Health and Retirement Study (2008 and 2010 waves) USA N = 10,912	Aged ≥ 50 (mean F 67.6, mean M 66.7) F: 58.9 %	11-item loneliness scale. Responses scored and mean was used (score 1 = hardly ever lonely; 1–1.99 sometimes lonely; ≥ 2 often lonely) Sometimes lonely M 68.1 %; F 67.0% Often lonely M 19.1 %; F 16.8 %	hsCRP High CRP ≥ 3.0 μg/L M 19.5 % high CRPF 27.4 % high CRP	ELISA Dried blood spot analysis	Logistic regression	Age, sex (referred to as gender), ethnicity, Education, Marital Status, Smoking status, and Disease (Diabetes, Chronic lung disease, Heart disease, Arthritis).	**Sometimes lonely** OR 1.24 (1.05–1.46), p = .014 **Often lonely** OR 1.44 (1.16–1.79), p = .001	**Sometimes lonely** OR 1.17 (0.98–1.41), p = .08 **Often lonely** OR 1.14 (0.97–1.56), p = .09
Rueggeberg et al., 2012	Montreal Ageing and Health Study Canada N = 122	Aged 60 + (mean 71.61, SD 5.00) F: 50.8 %	Two questions asking about the extent to which they felt 'lonely' or 'isolated' at the end of three non-consecutive days. Rated on 5 point Likert scale from very slightly/not at all (0) to extremely (4). 30.3 % reported some loneliness over three days	CRP	ELISA Not stated whether fasting, dried blood spot analysis	A.) Correlation B.) Simple regression (loneliness at baseline and CRP at 6-year follow-up)		A.) *r* = 0.04, ns B.) β = 0.01, ns	
Shankar et al., 2011	English Longitudinal Study of Aging UK N = 5,009 (CRP) 5,866 (Fibrinogen).	Aged 50+ (mean 66.9, SD 10.4) F: 53.9 %	3-item UCLA loneliness scale. Scores ranged from 3 to 9, greater scores indicative of more loneliness. Loneliness mean 4.2, SD 1.4	CRP Fibrinogen *People with CRP > 10 mmol/L or people who reported any respiratory illness 3 weeks prior to study removed for CRP analysis*	CRP: Immunoassay Fibrinogen: Clauss thrombin clotting method Blood draw protocol not specified	Multiple linear regression (log-transformed CRP)	Age, sex (referred to as gender), depression, limiting long-standing illness, marital status-adjusted wealth, social isolation.	–	**CRP** β = 0.02 (-0.03 to 0.06), ns **Fibrinogen** β = 0.01 (-0.01 to 0.02), ns
Shiovitz-Ezra and Parag, 2018	National Social Life, Health and Aging Project (Wave 1	Aged 57–85 (60–65 28.0%; 65–69 24.1%;	Single item CES-D (How often did you feel lonely in the past week?) scored from 0-4	CRP > 3 mg/dL high CRP	High sensitivity assays Blood draw protocol not specified	Logistic regression Predictor	Sex (referred to as gender), age, race, heart attack, stroke, cancer,	–	**Loneliness to some degree** OR 0.96, 95 %

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Table 1 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex AgeFemale (F)	LonelinessMeasure.Loneliness score.	InflammationMeasure Markers	 Assay methodBlood draw protocol	Statistical Analysis	Confounders adjusted	Results Least adjusted *(adjusted for maximum of 2 confounders)*	 Most adjusted
	2005-06 and Wave 2 2010-11) USA N = 1,815	70-74 19.9%; 75-79 17.9%; 80-85 10.2%) F: 52.9 %	Loneliness to some degree (scored 1–3) 29.4% Frequent loneliness (scored 2–3) 15.8%	*People with CRP > 10 mg/dL excluded*		loneliness at wave 1 and outcome CRP at wave 2	Antihypertensive medication, cholesterol medication, corticosteroid medication, antidepressant medication, alcohol drinking, currently smoking, wave 1 level of CRP		CI: 0.70, 1.33 **Frequent loneliness** OR 0.94, 95 % CI: 0.63, 1.39

Abbreviations: CES-D Centre for Epidemiological Studies Depression scale; CRP (C-reactive protein; ELISA (enzyme-linked immunosorbent assay; Hs (high-sensitivity; IL-Interleukin-; ; M (meanMCP-1 Monocyte Chemoattractant Protein-1; ; SD (standard deviation.

assessed heterogeneity using the Cochrane-*Q* statistic and the I^2 inconsistency index. A Cochrane-*Q* statistic with a p-value < .10 indicates that individual effects are further away from the common effect than we might expect due to chance. The I^2 statistic indicates the percentage of variability in the effect measure due to variation across studies with 25 % indicating low variability, 50 % indicating medium variability and 75 % indicating high variability. Publication bias was assessed with Egger's regression intercept test and plotted graphically with Funnel plots.

Sources of heterogeneity were explored using stratified sensitivity analyses to determine how robust the overall effect size was to sources of population, methodological, and statistical heterogeneity.

All analyses were performed with Comprehensive Meta-Analysis Software (version 3.0 Biostat, Englewood, NJ, USA).

3. Results

3.1. Study selection

After excluding duplicates, we retrieved 7,400 articles. In a first step, we screened the titles of articles and removed any papers that were not relevant based on broad criteria e.g., the study was in animals. Following this, we screened the abstracts of the remaining 525 studies, and removed those studies that we could determine did not meet inclusion criteria e.g., the age of the population, not examining inflammation, not a primary research study leaving us with 163 studies see Fig. 1). The remaining studies were put forward for full-text assessment, following which 136 studies were excluded (reasons are listed in Fig. 1). Inter-rater agreement for study screening at phase 3 was found to be very good (κ = 0.81, 95 % CI: 0.69, 0.93). Following an update search in July 2019, we were able to identify an additional three papers to include in the synthesis. Results are discussed with reference to those studies that examined loneliness and social isolation below.

3.2. Loneliness and inflammation

A total of 14 papers with data for 27,246 participants were identified that examined the association between loneliness and inflammation (see Table 1). The inflammatory markers examined in these studies included CRP, fibrinogen, IL-1RA, IL-6 and MCP-1.

3.2.1. CRP

The most commonly investigated inflammatory marker was the acute-phase protein CRP with eleven studies examining the association of loneliness with CRP (n = 24,790). Of those 11 studies, five provided only a least adjusted estimate, three provided only a fully-adjusted estimate and three provided both unadjusted and adjusted estimates (see Table 1). Of the eight studies that examined an unadjusted association between loneliness and CRP, three found a significant positive association (Cho et al., 2015; Nersesian et al., 2018; Pavela et al., 2018). However, of the seven studies that provided a most-adjusted estimate, only one study conducted in 927 people from the Midlife in the US study found a significant association (Nersesian et al., 2018).

Random effects meta-analyses found that there was not an association between loneliness and CRP when synthesising the least adjusted (r = 0.047, 95 % CI: -0.003-0.098, p = .067) or most adjusted estimates (r = 0.023, 95 % CI: -0.018-0.065, p = .27) (see Fig. 2a and b). Both the I^2 and Cochrane-*Q* statistics indicated moderate-high statistical heterogeneity, however there was no evidence of publication bias for either analysis when assessed using Egger's test (see Appendix III).

3.2.2. Fibrinogen

Four studies examined the association between loneliness with the acute-phase protein fibrinogen n = 7,612, with three providing both

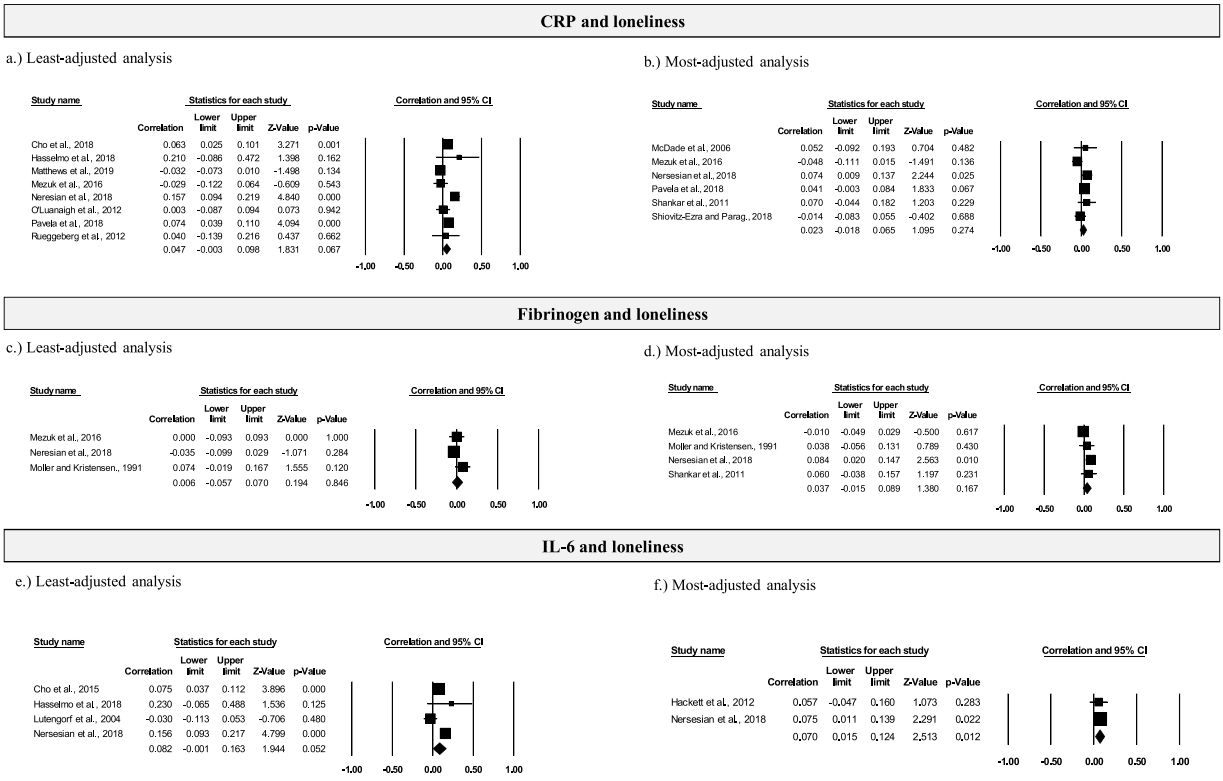

Fig. 2. Forest plots of association between loneliness with CRP, Fibrinogen and IL-6.

unadjusted and adjusted estimates B. Mezuk et al., 2016; Moller and Kristensen, 1991; Nersesian et al., 2018) and one paper providing only an adjusted estimate (Shankar et al., 2011). Only the study of Nersesian et al. (2018) conducted in the Midlife in the US sample found an association between loneliness and fibrinogen, all other studies found null associations (see Table 1).

Results from random effects meta-analyses indicated that there was neither an unadjusted (r = 0.006, 95 % CI: -0.057, 0.070, p = 0.846) or confounder adjusted (r = 0.037, 95 % CI: -0.015, 0.089; p = .167) association between loneliness with fibrinogen (see Fig. 2c and d). The I^2 and Cochrane-Q statistics both indicated moderate heterogeneity and there was no evidence of publication bias when assessed using Egger's test or by visually inspecting funnel plots (see Appendix III).

3.2.3. IL-6

Five studies n = 4,692 examined IL-6 with three providing unadjusted estimates, one adjusted estimates only and one both unadjusted and adjusted estimates see Table 1). Of the four studies examining an unadjusted association, two found a significant association (Cho et al., 2015; Nersesian et al., 2018). Of the two studies providing a most-adjusted estimate, only one found a significant association (Nersesian et al., 2018).

Results from the random effects meta-analyses indicated there was a borderline non-significant least-adjusted association between loneliness with IL-6 (r = 0.082, 95 % CI: -0.001, 0.163, p = .052). However, there was evidence of a significant most-adjusted association (r = 0.070, 95 % CI: 0.015, 0.124, p = .012) (see Fig. 2e and f). Heterogeneity statistics indicated high heterogeneity for the unadjusted estimate with no publication bias evident using Egger's test or when inspecting funnel plots (see Appendix III). However, there was low heterogeneity with no publication bias for the most-adjusted estimate (see Appendix III).

3.2.4. Other inflammatory markers

Only one study examined IL-1RA and the chemokine MCP-1 (Hackett et al., 2012). They did not find an adjusted association between IL-1RA with loneliness though they did find a significant association between MCP-1 and loneliness using data from 524 civil servants from the Whitehall II study (Hackett et al., 2012). As only one study examined these inflammatory markers, these data were not assessed using meta-analysis.

3.2.5. Study heterogeneity

There was methodological heterogeneity between studies in terms of population studied, loneliness measurement, inflammation measurement, statistical analysis and study quality (see Table 1 and Appendix IV). Study heterogeneity was explored qualitatively and quantitatively with sensitivity analyses. Sensitivity analyses could not be performed for the most-adjusted IL-6 estimate as only two studies were included.

3.2.6. Populations studied

The majority of studies were conducted in the USA, with an additional three studies being conducted in the UK, and one each in Denmark, Ireland and Canada (see Table 1 and Appendix IV). The most commonly investigated populations were middle-aged and older adult community samples with only one study examining younger adults (see Table 1 and Appendix IV).

Sensitivity analyses for different aspects of the population studied for fibrinogen and IL-6 revealed that the non-significant associations remained consistent (see Table 2). However, for the least-adjusted association between loneliness and CRP significant associations were seen for those studies conducted in US samples (r = 0.077, 95 % CI: 0.027, 0.126, p = .002), and those studies conducted in people 35 and older (r = 0.063, 95 % CI: 0.018, 0.106, p = .005) or 50 and older (r = 0.062, 95 % CI: 0.025, 0.098, p = .001). These significant associations were not observed in the most-adjusted sensitivity analyses for loneliness and CRP.

3.2.7. Loneliness measurement

A total of seven studies used the full or shortened versions of the

Table 2
Sensitivity analyses for associations of loneliness with CRP, fibrinogen and IL-6.

		CRP		Fibrinogen		IL-6	
		Least-adjusted*r* (95% CI)	Most-adjusted*r* (95% CI)	Least-adjusted*r* (95% CI)	Most-adjusted*r* (95% CI)	Least-adjusted*r* (95% CI)	Most-adjusted*r* (95% CI)
Population	Largest study removed	r = 0.042 (-0.021, 0.105) p = .193	r = 0.019 (-0.036, 0.073), p = .508	r = 0.037 (-0.036, 0.110) p = .320	r = 0.034 (-0.032, 0.100), p = .311	r = 0.095 (-0.064, 0.249) p = .242	N/A
	USA samples only	r = 0.077 (0.027, 0.126), p = .002	r = 0.018 (-0.028, 0.064), p = .438	r =-0.024 (-0.077, 0.029), p = .378	r = 0.035 (-0.060, 0.130), p = .473	All studies: r = 0.082 (-0.001, 0.163), p = .052	N/A
	Community samples only	r = 0.053 (-0.002, 0.109), p = .060	All studies: r = 0.023 (-0.018, 0.065), p = .274	All studies: r = 0.006 (-0.057, 0.070), p = 0.846	All studies: r = 0.038 (-0.016, 0.091), p = 0.167	All studies: r = 0.082 (-0.001, 0.163), p = .052	N/A
	People aged 50 or older	r = 0.062 (0.025, 0.098), p = .001	r = 0.031 (-0.004, 0.065), p = .079	N/A: Only Moller and Kristensen (1991)	R = 0.048 (-0.020, 0.116), p = .162	N/A: Only Lutengorf et al (2004)	N/A
Loneliness assessment	Loneliness questionnaire	r = 0.031 (-0.025, 0.087), p = .283	r = 0.019 (-0.038, 0.076), p = .514	r =-0.024 (-0.077, 0.029), p = .378	r = 0.010 (-0.052, 0.072), p = .754	r = 0.048 (-0.050, 0.144), p = .338	N/A
	Single-item questionnaire	r = 0.075 (-0.041, 0.189), p = .205	r = 0.010 (-0.037, 0.057), p = .663	N/A	r = 0.071 (0.017, 0.125), p = .011	N/A: Only Nersesian et al (2018)	N/A
	Moderate levels of loneliness versus no loneliness	r = 0.009 (-0.062, 0.080), p = .801	r =-0.015 (-0.106, 0.076), p = .739	N/A: Only Mezuk et al (2016)	N/A: Only Mezuk et al (2016)	N/A	N/A
	High levels of loneliness versus no loneliness	r = 0.039 (-0.043, 0.121), p = .347	r = 0.030 (-0.012, 0.072), p = .163	N/A: Only Mezuk et al (2016)	N/A: Only Mezuk et al (2016)	N/A	N/A
Inflammation assessment	High levels inflammation/ people with inflammatory conditions or taking inflammatory medications accounted for: yes	N/A: Only Hasselmo et al (2018)	r = 0.015 (-0.040, 0.069), p = .601	N/A	r = 0.008 (-0.052, 0.067), p = .799	N/A: Only Hasselmo et al (2018)	N/A
	High levels inflammation/ people with inflammatory conditions or taking inflammatory medications accounted for: no	r = 0.043 (-0.008, 0.094), p = .100	r = 0.011 (-0.043, 0.065), p = .690	All studies: r = 0.006 (-0.057, 0.070), p = 0.846	r = 0.069 (0.016, 0.122), p = .010	r = 0.071 (-0.015, 0.156), p = .104	N/A
	Blood draw protocol that accounted for confounders: yes	r = 0.093 (-0.063, 0.244), p = .242	r =-0.008 (-0.087, 0.070), p = .836	r =-0.024 (-0.077, 0.029), p = .378	r = 0.033 (-0.058, 0.125), p = 0.476	r = 0.095 (-0.064, 0.249), p = .242	N/A
	Blood draw protocol that accounted for confounders: no	r = 0.031 (-0.019, 0.082), p = .226	r = 0.031 (-0.004, 0.065), p = .079	N/A: Only Nersesian et al (2018)	r = 0.048 (-0.020, 0.116), p = .162	N/A: Only Cho et al (2015)	N/A
Statistical analyses	Linear analyses (linear predictor and outcome)	r = 0.031 (-0.047, 0.109), p = .437	r = 0.009 (-0.074, 0.093), p = .828	N/A: Only Moller and Kristensen (1991)	r = 0.008 (-0.031, 0.047), p = .688	r = 0.048 (-0.050, 0.144), p = .338	N/A
	Linear analyses log transformed: yes	r =-0.028 (-0.068, 0.012), p = .173	All linear analyses: r = 0.009 (-0.074, 0.093), p = .828	N/A: Only Moller and Kristensen (1991)	All linear analyses: r = 0.008 (-0.031, 0.047), p = .688	All linear analyses: r = 0.048 (-0.050, 0.144), p = .338	N/A
	Linear analyses log transformed: no	r = 0.065 (0.028, 0.103), p = .001	N/A	N/A	N/A	N/A	N/A
	Categorical analysis (lonely versus non-lonely)	r = 0.059 (-0.012, 0.129), p = .102	r = 0.036 (-0.008, 0.079), p = .107	r =-0.024 (-0.077, 0.029), p = .378	N/A	N/A: Only Nersesian et al (2018)	N/A
	All important confounders controlled for: yes	N/A	r =-0.010 (-0.057, 0.036), p = .665	N/A	r = 0.035 (-0.060, 0.130), p = .473	N/A	N/A
	All important confounders controlled for: no	N/A	r = 0.045 (0.006, 0.084), p = .024	N/A	r = 0.048 (-0.020, 0.116), p = .162	N/A	N/A
Quality assessment	High quality studies	r = 0.074 (-0.009, 0.156), p = .082	r = 0.023 (-0.042, 0.088), p = .485	r =-0.024 (-0.077, 0.029), p = .378	r = 0.033 (-0.058, 0.125), p = .476	N/A: Only Nersesian et al (2018)	N/A
	Moderate quality studies	r = 0.022 (-0.047, 0.091), p = .525	r =-0.015 (-0.040, 0.069), p = .601	N/A: Only Moller and Kristensen (1991)	r = 0.048 (-0.020, 0.116), p = .162	r = 0.048 (-0.050, 0.144), p = .338	N/A
	Low quality studies	N/A	N/A	N/A	N/A	N/A	N/A

For the most-adjusted IL-6 analysis we could not conduct any sensitivity analyses as only two studies were included in that synthesis: Nersesian et al (2018) and Hackett et al (2012).
For all other analyses:
N/A with no named studies indicates that there was no eligible data, and the sensitivity analysis could not be performed.
N/A with a named study indicates only the named study was eligible, and the sensitivity analysis could not be performed.

Table 3
Studies examining the association between social isolation with inflammation.

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex. Age% Female %	Social isolationMeasure.Social isolation score.	Inflammation Measure		Statistical Analysis	Confounders adjusted	Results	
				Inflammatory markers	Assay method Blood draw protocol			Least adjusted *(adjusted for maximum of 2 confounders)*	Most adjusted
Das, 2013	National Social Life, Health and Aging Project USA N = 878 inflammation data (total n = 1455)	Age: 57–85 (mean 67.55, SE 0.28) F: 0%	Fewer alters (number of people in social network 0-6 higher numbers fewer alters) Mean alters 2.74	CRP *(> 8.6 mg/l excluded)*	High sensitivity assays Dried blood spots: no limits specified	OLS regression models	Age, education, lifetime diagnosis of diabetes, hypertension.	–	Coeff 0.00 (0,02), ns
Ford et al., 2006	NHANES III USA N = 14, 818	Aged ≥ 20 (mean 44.0, SE 0.4) F: 53.1 %	Social network index based on Berkman Syme Index given 1 point for each of following (married, ≥ 156 contacts per annum with friends, family or neighbours, ≥ 4 visits per annum to church and belonging to any club or group. Score of ≤ 1 low social integration Males 22.7 % low social integration. Females 17.8 % low social integration	CRP (> 3 mg/L high CRP)	Latex enhanced nephelometry No limits placed on when samples were drawn or fasting	A.) Chi-squared analysis B.) Logistic regression (reference group: most ties)	Age, ethnicity, education, smoking status, alcohol use, physical activity, BMI, hypertension, total cholesterol, self-reported diabetes.	A.) **Male** SNI 0–1: 25.4% SNI 1: 22.9 % SNI 2: 19.1 % SNI 4: 17.7 % P < .001 **Female** SNI 0–1: 35.1% SNI 1: 31.3 % SNI 2: 31.3 % SNI 4: 28.6 % P = .025	B.) **Male** Fewest ties aged 20-59: OR: 0.93 (0.62–1.39) Fewest ties aged ≥ 60: OR 1.80 (1.11–2.92) **Female** Fewest ties aged 20-59: OR: 1.22 (0.85–1.76) Fewest ties aged ≥ 60: OR 0.91 (0.57–1.46)
Glei et al., 2012	A.) Midlife in the US National Study USA N = 990 B.) Social Environment and Biomarkers of Aging Taiwan N = 962	A.) Aged 35–86 (mean 57.9, SD 11.5) F: Not specified B.) Aged ≥ 50 (mean 65.2, SD 9.1) F: Not specified	Social integration score based on Berkman-Syme Index given 1 point for each of following (married or living with partner/ companion; minimum weekly contact with at least one non-resident family member and one neighbour/friend; attended church/temple at least once per week; participated in other social group). Score of ≤ 1 low social integration A.) 15.6 % low social integration B.) 14.7 % low social integration	A.) CRP IL-6 Fibrinogen *People with CRP > 10* mg/dL *excluded*	A.) CRP: Immunoturbidimetry IL-6 ELISA Fibrinogen: Coagulation Method B.) CRP: Immunoturbidimetry IL-6: ELISA Fibrinogen: Immunoturbidimetry Both studies took fasting blood draw	Multiple linear regression (reference: not isolated)	Age, sex (referred to as gender), education, mainlander status (B only), waist circumference, hypertensive medication, lipid lowering medication, hormone/steroid medication, self-rated health, depression, smoking status, whether drinks alcohol, social support, functional limitations.	–	**A.)** CRP: β = -0.08, ns IL-6: β = -0.04, ns Fibrinogen: β = -0.11, ns **B.)** CRP: β = -0.15, ns IL-6: β = 0.11, ns Fibrinogen: β = 0.15, ns
Hafner et al., 2011	MONIKA/ KORA Germany N = 1547	Age: 35–74 F: 45.25 %	Social network index (lowest quartile of scores identified as socially isolated) M: 9.2 % socially isolated F: 13.9 % socially isolated	hsCRP IL-6	hsCRP: Immuno-radiometric assay IL-6: ELISA No blood draw protocol specified	Multiple linear regression	Age, survey year, BMI, smoking, alcohol and physical activity.	**Male** CRP: β -0.266 (0.17), p = .115 IL-6: β 0.104 (0.16), p = .505 **Female**	**Male** CRP: β -0.265 (0.16), p = .091 IL-6: β 0.111 (0.15), p =

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Table 3 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex. Age% Female %	Social isolationMeasure.Social isolation score.	Inflammation Measure		Statistical Analysis	Confounders adjusted	Results	
				Inflammatory markers	Assay method Blood draw protocol			Least adjusted *(adjusted for maximum of 2 confounders)*	Most adjusted
								CRP: β -0.161 (0.16), p = .305 IL-6: β -0.020 (0.14), p = .889 *Nb: Adjusted for age and survey*	.469 **Female** CRP: β -0.151 (0.14), p = .284 IL-6: β 0.003 (0.14), p = .985
Heffner et al., 2011	Community sample USA N = 327 (of total sample of 2321)	Mean age 55.5, SD 9.8 F: 61.2 %	Social integration index (marital status, contact with social network, religious affiliation and participation in community groups) Scores ranged 0-4 and score 0-1 indicated social isolation. 14.1 % socially isolated	CRP (> 3 mg/L high CRP)	Immuno-turbidimetric assay No blood draw protocol specified	A.) Means B.) Logistic regression (reference group: highest social integration)	Age, BMI, income	A.) Lowest social integration: M: 10.83 pg/mL, SD 2.27 Low-moderate social integration: M 3.28 pg/mL, SD 1.67 Moderate-high social integration: M 4.88 pg/mL, SD 1.51 Highest social integration: M 4.00 pg/mL, SD 1.40 B.) OR: 2.32 (1.16–4.66)	B.)OR: 2.69 (1.26–5.75)
Helminen et al., 1997	Community sample Finland N = 193	Aged 50-60 (mean 55.1 95% CI 54.7-55.5) F: 0% Ethnicity not reported	Created a social network index (included social anchorage, contact frequency, social participation and adequacy of social participation). Lowest tertile of scores defined as weak participation.	Fibrinogen	Thrombin time method Bloods taken between 7.30–10 am after 12 hour fast and 30 minutes supine. Participants advised not to take anti-inflammatory medication prior to blood draw.	Students t-test	–	Weak network: M 3.36 g/l, SD 0.49 Strong network: M 3.26 g/l, SD 0.57 p = .237	–
Lacey et al., 2014	National Child Development Study in Great Britain UK N = 6632 with data for social isolation of total 7462 (data mentioned as mainly imputed)	Adult Social isolation measured at 33, CRP measured at 44. F: 49.5 %	Created a social isolation index (asked to list up to four people who could help in six situations) responses summed and those who reported ≤ 3 sources of support were identified as socially isolated. 19.3 % socially isolated	CRP *(participants with ≥ 10 mg/L removed from analysis)*	High-sensitivity nephelometric analysis No blood draw protocol specified	Multiple linear regression	Childhood social isolation, sex (referred to as gender), childhood BMI, parental divorce.	–	β = 0.001, p = ns

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Table 3 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex. Age% Female %	Social isolationMeasure.Social isolation score.	Inflammation Measure		Statistical Analysis	Confounders adjusted	Results	
				Inflammatory markers	Assay method Blood draw protocol			Least adjusted *(adjusted for maximum of 2 confounders)*	Most adjusted
Loucks et al., 2005	MacArthur Successful Ageing Study USA N = 800	Aged 70–79 (F mean 74.4, SD 2.7; M mean 74.1, SD 2.7) F: 53.13 %	Created a social network score with six variables (presence of spouse, number of close relatives, number of close friends, frequency of participation in religious activities, frequency of participation in clubs). Scores ranged from 0-6 and were split into quartiles, the lowest scoring quartile (0-2) represented the smallest network.	Fibrinogen (> 336 mg/dL high fibrinogen; highest quartile)	Automated clot-rate assay Blood samples collected 8am	Logistic regression (reference group: highest scoring social network quartile)	Age, education, race, smoking, alcohol consumption, physical activity, BMI, co-morbid health conditions, physical functioning, depression.	**Male** OR 2.40 (1.21–4.75), p = .01 **Female** OR 0.78 (0.40–1.50), p.31	**Male** 2.29 (1.07–4.89), p = .03 **Female** OR 0.57 (0.27–1.21), p = .15
Loucks et al, 2006**a** ***nb: Same sample as above but included as examines different inflammatory markers***	MacArthur Successful Ageing Study USA N = 805	Aged as above F: 52.80 %	Social network index as calculated above	IL-6 (> 4.64 pg/ml defined as high IL-6, highest quartile) CRP (> 3.19 mg/L defined as high CRP, highest quartile)	ELISA Blood samples collected 8am	Logistic regression (reference group: highest scoring social network quartile)	Age, race, socioeconomic status, cardiovascular disease, other major/ chronic conditions (diabetes, high blood pressure, cancer, and broken bones), physical functioning, depression, smoking, alcohol consumption, physical activity, BMI, depression	**Male** CRP: OR 2.18 (1.17–4.42), p < .05 IL-6: OR 1.45 (0.74–2.85), ns **Female** CRP: OR 1.00 (0.52–1.95), ns IL-6: OR 1.12 (0.57–2.19), ns	**Male** IL-6: OR 1.30 (0.61–2.79), ns CRP: OR 2.23 (1.05–4.76), P < .05 **Female** CRP: OR 0.93 (0.43–1.99), ns IL-6: OR 0.93 (0.44–1.97), ns
Loucks et al, 2006**b**	Framingham Heart Offspring Study USA N = 3129 (CRP analysis) and N = 3125 (IL-6 analysis)	Mean age 62, SD 10 F 46.0 % Ethnicity not reported	Questions based on Berkman-Syme Index (whether married, had close friends and relatives, participated in groups or religious meetings). Scores ranged from 0-4 and a score of 0-1 was identified as those most isolated.	CRP IL-6	CRP: High sensitivity assay IL-6: ELISA Fasting blood draw	Multiple linear regression (reports mean levels at different levels of social integration)	Age, smoking, systolic blood pressure, total: HDL-cholesterol ratio, BMI, lipid-lowering medication, antihypertensive medication, diabetes, CVD, depression, education.	**Male** **CRP** Quintile 1: Most isolated mean 3.82 mg/l, SD 0.57 Quintile 2: mean 3.72 pg/mL, SD 0.41 Quintile 3: mean 3.39 pg/mL, SD 0.44 Quintile 4: Least isolated mean 3.37 mg/l, SD 0.54 p = .08 **IL-6** Quintile 1: Most isolated mean 4.15 pg/mL, SD 0.36 Quintile 2: mean 4.10 pg/mL, SD 0.25 Quintile 3: mean 3.68 pg/mL, SD	**Male** **CRP** Quintile 1: Most isolated mean 3.18 mg/l, SD 0.62 Quintile 2: mean 3.41 pg/mL, SD 0.43 Quintile 3: mean 3.09 pg/mL, SD 0.46 Quintile 4: Least isolated mean 3.34 mg/l, SD 0.57 p = .96 **IL-6** Quintile 1: mean 3.85 pg/mL, SD 0.38 Quintile 2: mean 3.97 pg/mL, SD 0.27 Quintile 3: mean 3.59 pg/mL, SD 0.28

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Table 3 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex. Age% Female %	Social isolationMeasure.Social isolation score.	Inflammation Measure		Statistical Analysis	Confounders adjusted	Results	
				Inflammatory markers	Assay method Blood draw protocol			Least adjusted *(adjusted for maximum of 2 confounders)*	Most adjusted
								0.27 Quintile 4: Least isolated mean 3.43 pg/Ml, SD 0.33 p = .0001 **Female** **CRP** Quintile 1: Most isolated mean 4.85 mg/l, SD 0.39 Quintile 2: mean 4.69 pg/mL, SD 0.29 Quintile 3: mean 4.74 pg/mL, SD 0.26 Quintile 4: Least isolated mean 4.79 mg/l, SD 0.32 p = .99 **IL-6** Quintile 1: Most isolated mean 3.98 pg/mL, SD 0.27 Quintile 2: mean 3.51 pg/mL, SD 0.20 Quintile 3: mean 3.45 pg/mL, SD 0.18 Least isolated mean 3.47 pg/Ml, SD 0.22 p = .03	Quintile 4: Least isolated mean 3.52 pg/mL, SD 0.35 p = .03 **Female** **CRP** Quintile 1: Most isolated mean 3.90 mg/l, SD 0.38 Quintile 2: mean 3.86 pg/mL, SD 0.28 Quintile 3: mean 4.15 pg/mL, SD 0.264.79 Quintile 4: Least isolated mean 4.21 mg/l, SD 0.31 p = .20 **IL-6** Quintile 1: Most isolated mean 3.64 pg/mL, SD 0.28 Quintile 2: mean 3.33 pg/mL, SD 0.21 Quintile 3: mean 3.43 pg/mL, SD 0.19 Quintile 4: Least isolated mean 3.38 pg/Ml, SD 0.23 p = .39
Mezuk et al., 2010	Multi-ethnic study of Ather-sclerosis USA N = 6814	Aged 45–85 (mean 61.9) F:53 %	Emotional social support index (frequency of support across 6 items). Low support < 12, moderate support 12-24, high support ≥ 25. 2.6% low social support	CRP Fibrinogen IL-6	CRP: nephlometry Fibrinogen: nephlometry IL-6: ELISA Fasting blood samples	Multiple linear regression (reference group high support) *Nb for quantitative synthesis means found in the paper were used*	Age, sex (referred to as gender), ethnicity, education, income, employment status, marital status, smoking status, alcohol use, BMI, hypertension, diabetes, medication use and recent. infection	**CRP** B = 0.21 (95 % CI 0.04, 0.37), p < .05 **Fibrinogen** B = 0.04 (95 % CI 0.01, 0.08), p < .05 **IL-6** B = 0.13 (95 %	**B.)** **CRP** B = 0.15 (95 % CI -0.01, 0.30), p < .05 **Fibrinogen** B = 0.03 (95 % CI -0.01, 0.06), ns **IL-6**

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Table 3 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex. Age% Female %	Social isolationMeasure.Social isolation score.	Inflammation Measure		Statistical Analysis	Confounders adjusted	Results	
				Inflammatory markers	Assay method Blood draw protocol			Least adjusted *(adjusted for maximum of 2 confounders)*	Most adjusted
						for least-adjusted synthesis		CI 0.03, 0.24), p < .05	B = 0.06 (95 % CI -0.04, 0.15), ns
Nagayoshi et al., 2014	Althero-sclerotic Risk in Communities Study USA N = 13,686	Mean age 57 F: 56 %	Lubben Social Network Scale Small social network ≤ 20 2.8% small social network	hsCRP	Latex-particle-enhanced-immuno- turbidimetric assay No information about blood draw protocol	Means	–	Small social network: M: 5.0 mg/dL, SD 8.6 Moderately small social network: M 4.6 mg/dL, SD 8.7 Moderately large social network: M 4.3 mg/dL, SD 6.4 Large social network: M 4.3 mg/dL, SD 6.7	
Rosengren and Wilhelmsen, 1996	The Study of Men Born in 1933 Sweden N = 664 (of 1016)	Aged 50 F: 0%	Interview schedule for Social Interaction: social networks/ social integration component. Scores split into groups (lowest integration = bottom 25 %; intermediate integration = middle 50%; high integration = top 25%) 20.6 % low integration	Fibrinogen	Polymerization method (Clauss assay) Fasting blood sample	Simple regression	–	Low integration: 3.31 g/l, SD 0.74 Intermediate integration: 3.13 g/l, SD 0.80 High integration: 3.00 g/l, SD 0.74 p = 0.010	–
Shankar et al., 2011	English Long-itudinal Study of Aging UK N = 5,009 (CRP) 5,866 (Fibrinogen).	Aged 50+ (mean 66.9, SD 10.4) F: 53.9 %	Social isolation index (not married/cohabiting, less than monthly contact with friends, family or relatives and participation in organisations/ community groups). Scores ranged from 0 to 5 with higher scores more isolated. Social isolation mean 1.6, SD 1.4	CRP Fibrinogen	CRP: Immunoassay Fibrinogen: Clauss thrombin clotting method	Multiple linear regression No blood draw protocol specified	Age, sex (referred to as gender), depression, limiting long-standing illness, marital status-adjusted wealth, loneliness.	–	**CRP** β = 0.05 (0.003 to 0.09), p < .05 **Fibrinogen** β = 0.002 (-0.01 to 0.02), p < .001
Steptoe et al., 2003	Whitehall II UK N = 221	Aged 47-58 F: 43.44 %	Close persons question-naire (contact with friends, family and relatives at least once a month) scored 0-3 with higher scores indicating more isolation. Scores of 1-3 indicative of social isolation 42.7%–51.4% socially isolated.	Fibrinogen	Automated Clauss Assay Prohibited from drinking caffeinated drinks, or smoking 2 hours prior to testing. Also prohibited from vigorous exercise or consuming alcohol the day before the study.	ANOVA	Hematocrit	Isolated group: M 2.99 g/l, SD 0.06 Non-isolated group: 2.81 g/l, SD 0.51 *Nb: Hematocrit adjusted means*	
Yang et al., 2013 ***(note same sample as Ford et al but examined different biomarkers)***	NHANES III USA N = 6729	Aged 40+ 40–64: 55.18% ≥ 65: 44.82 F: 54.20 %	Berkman Syme Index (scores 0–4) scores of 0–1 socially isolated M: 18.6 % isolatedF: 16.2 % isolated	Fibrinogen Albumin	Fibrinogen: Clauss clotting methods Albumin: DcX800 method No blood draw protocol specified	Logistic regression	Age, race-ethnicity, education, family income, smoking, drinking, physical activity, BMI, chronic	**Male** Fibrinogen OR 1.94 (1.44–2.62), p < .001	**Male** Fibrinogen OR 1.68 (1.21–2.30), p < .01

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Table 3 (*continued*)

First author, year	Study name, Sampling, Country, N	Baseline Sample Age, Sex. Age% Female %	Social isolationMeasure.Social isolation score.	Inflammation Measure		Statistical Analysis	Confounders adjusted	Results	
				Inflammatory markers	Assay method Blood draw protocol			Least adjusted *(adjusted for maximum of 2 confounders)*	Most adjusted
							conditions, self-rated health.	Albumin OR 1.03 (0.77–1.36), ns **Female** Fibrinogen OR 1.38 (1.08–1.78), p < .05 Albumin OR 0.88 (0.69–1.13), ns *Nb: Adjusted for age and race-ethnicity*	Albumin Male OR 0.93 (0.70–1.24), ns **Female** Fibrinogen OR 1.17 (0.90–1.53), ns Albumin OR 0.84 (0.65–1.08), ns

Abbreviations: ANOVA (Analysis of Variance); CRP (C-reactive protein); ELISA (enzyme-linked immunosorbent assay); Hs (high-sensitivity); IL-(Interleukin-); M (mean); SD (standard deviation).

UCLA-loneliness scale, with two studies utilising other loneliness questionnaires (see Table 1 and Appendix IV). The remaining studies used either one or two single-item self-rated questions (see Table 1 and Appendix IV).

Sensitivity analyses indicated that the associations between loneliness with CRP and IL-6 were not affected by loneliness measurement in either unadjusted or adjusted analyses (see Table 2). However, sensitivity analyses examining fibrinogen revealed that the most-adjusted non-significant association between loneliness with fibrinogen was significant when only those studies that used a single-item loneliness question were synthesised (r = 0.071, 95 % CI: 0.017, 0.125, p = .011).

3.2.8. Inflammation measurement

All studies employed a standardised protocol for assessing blood samples, however blood draw protocols did differ between studies (see Table 1 and Appendix IV). Only one study prohibited people from engaging in a variety of activities known to influence inflammation prior to the blood draw such as drinking caffeine and exercise (Hackett et al., 2012). Five studies mentioned that fasting bloods were taken or that bloods were taken at a particular time of day (see Table 1 and Appendix IV). However, nine studies did not mention any limits on blood collection.

Sensitivity analyses indicated that associations between loneliness with CRP and IL-6 were not changed based on inflammation measurement (see Table 3). When synthesising the most-adjusted fibrinogen studies that did not exclude people based on high levels of inflammation or inflammatory conditions there was a significant association (r = 0.069, 95 % CI: 0.016, 0.122, p = .010). All other fibrinogen sensitivity analyses remained non-significant (see Table 2).

3.2.9. Statistical analysis

A variety of statistical methodologies were employed by the researchers. Eleven studies examined inflammation as a continuous outcome using either correlational analyses and/or linear regression analyses. However, only seven of these studies checked the normality of their data prior to running their analyses (see Appendix IV). Furthermore, confounder control was mixed with only three of the seven studies that controlled for confounders accounting for all important confounders (see Appendix IV). Finally, three studies provided estimates that accounted for the level of loneliness, finding no difference in results based on whether someone was sometimes or often lonely (B. Mezuk et al., 2016; Pavela et al., 2018; Shiovitz-Ezra and Parag, 2018).

Sensitivity analyses indicated that the associations between loneliness with fibrinogen and IL-6 remained consistent (see Table 2). However, a significant least adjusted association between loneliness and CRP was observed for those studies that employed linear analyses where CRP was not log transformed (r = 0.065, 95 % CI: 0.028, 0.103, p = .001). Furthermore, a significant most-adjusted association between loneliness and CRP was observed for those studies that did not control for important confounders (r = 0.045, 95 % CI: 0.006, 0.084, p = .024).

3.2.10. Quality assessment

Results from the quality assessment tool indicated that study quality ranged from high to low (see Appendix II). In total, four studies were high quality (Mezuk et al., 2016; Nersesian et al., 2018; Pavela et al., 2018; Shankar et al., 2011), nine were moderate quality (Cho et al., 2015; Hackett et al., 2012; Hasselmo et al., 2018; Lutgendorf et al., 2004; Matthews et al., 2019; McDade et al., 2006; Moller and Kristensen, 1991; O'Luanaigh et al., 2012; Shiovitz-Ezra and Parag, 2018) and one study was low quality (Rueggeberg et al., 2012). The sources of bias most commonly seen across the included studies involved inadequate confounder control and studies not accounting for high levels of inflammation or confounders that could affect

inflammation (see Appendix II).

Sensitivity analyses indicated that the associations between loneliness with CRP, fibrinogen and IL-6 were not affected by study quality (see Table 2).

3.3. Social isolation and inflammation

A total of 16 different papers with data for 57,532 participants were included in the synthesis (see Table 3). Two papers used data from the NHANES III study, however they analysed different inflammatory markers with Ford et al. (2006) examining CRP and Yang et al. (2013) examining fibrinogen and albumin. Likewise two papers used data from the MacArthur Successful ageing study but examined different inflammatory markers and so were synthesised in separate analyses (Loucks et al., 2005, 2006). Finally, one study analysed data from two studies: Midlife in the US and Social Environment and Biomarkers of Aging Study (Glei et al., 2012).

The inflammatory markers examined included CRP, fibrinogen, albumin and IL-6. In total, eight of the included papers found a least-adjusted association and eight found a significant most-adjusted association between social isolation with inflammation (see Table 3).

3.3.1. CRP

The most commonly investigated inflammatory marker was CRP, which was assessed across 11 papers (n = 55,597). One paper provided means with no association (Nagayoshi et al., 2014), four provided only a confounder adjusted estimate (Das, 2013; Glei et al., 2012; Lacey et al., 2014; Shankar et al., 2011) and six provided both least adjusted and most adjusted estimates (Ford et al., 2006; Haefner et al., 2011; Heffner et al., 2011; Loucks, Berkman, et al., 2006; Loucks et al., 2006b; Mezuk et al., 2010).

Of the six studies that provided a least adjusted estimate five found at least one significant association between social isolation with CRP (Ford et al., 2006; Haefner et al., 2011; Loucks et al., 2006a, b; Mezuk et al., 2010). Of the 11 studies that provided a most adjusted estimate, five found at least one significant association between social isolation with CRP (Ford et al., 2006; Heffner et al., 2011; Loucks et al., 2006a; Mezuk et al., 2010; Shankar et al., 2011).

Results from random effect meta-analyses indicated a significant unadjusted association between social isolation and CRP (r = 0.186, 95 % CI: 0.063, 0.303; p = .003). However, results from the most adjusted synthesis indicated no association between social isolation and CRP once confounders were controlled for (r = 0.021, 95 % CI: -0.051, 0.092; p = .567) (see Fig. 3a and b). Heterogeneity estimates suggested there was high study heterogeneity, with no statistical evidence of publication bias (see Appendix V). However, visual inspection of the funnel plot indicated one outlying study with a notably larger effect size than other studies for the least-adjusted estimate (see Appendix V).

3.3.2. Fibrinogen

A total of nine studies (n = 23,239) examined the association between social isolation with fibrinogen. Of those nine studies one provided means with no measure of association (A. Steptoe et al., 2003), two provided least adjusted estimates only (Helminen et al., 1997; Rosengren and Wilhelmsen, 1996) and three provided both least and fully adjusted estimates (Loucks et al., 2005; Mezuk et al., 2010; Yang et al., 2013). Of the six studies that provided a least-adjusted estimate, four found a significant association between social isolation with fibrinogen (Loucks et al., 2005; Mezuk et al., 2010; Rosengren and Wilhelmsen, 1996; Yang et al., 2013). Of the six studies that provided a most-adjusted estimate, three found a significant association (Loucks et al., 2005; Shankar et al., 2011; Yang et al., 2013).

Random-effects meta-analyses found a significant association between social isolation with fibrinogen for the least-adjusted analysis (r = 0.103, 95 % CI: 0.043, 0.163; p = .001) and most-adjusted analysis (r = 0.039, 95 % CI: 0.011, 0.067; p = .007) (see Fig. 3c and d). The I^2 and Cochrane-Q statistics indicated high heterogeneity for the unadjusted analysis, and low-moderate heterogeneity for the most-adjusted analysis (see Appendix V). Egger's test and funnel plots suggested there was little evidence of publication bias (see Appendix V)

3.3.3. IL-6

A total of five papers (n = 14,423) examined the association between social isolation with IL-6. One paper provided only most-adjusted estimates (Glei et al., 2012) and four provided both least and most adjusted estimates (Haefner et al., 2011; Loucks et al., 2006a; Loucks et al., 2006b; Mezuk et al., 2010). Of the four studies that provided a least adjusted estimate, two found a significant association between social isolation and IL-6 (Loucks et al., 2006b; Mezuk et al., 2010). Of the five papers that provided a most-adjusted estimate, only Loucks et al. (2006b) found a significant association between social isolation and IL-6 in men from the Framingham heart study.

Results from the random-effects meta-analyses found no association between social isolation and IL-6 for the least-adjusted analysis (r = 0.267, 95 % CI: -0.341, 0.718; p = .393), or the most-adjusted analysis (r= -0.003, 95 % CI: -0.148, 0.141; p = .966) (see Fig. 3e and f). There was evidence of high heterogeneity for both estimates (see Appendix V). Furthermore, while Egger's test did not indicate publication bias, visual inspection of the funnel plot indicated that for the most-adjusted analysis all studies lay outside the funnel indicating heterogeneity (see Appendix V).

3.3.4. Other inflammatory markers

Yang et al. (2013) also examined albumin in their analysis of the NHANES III study, and found no association between social isolation with this inflammatory marker. As this was the only study that examined albumin, it was not put forward for meta-analysis.

3.3.5. Study heterogeneity

There was heterogeneity between studies for population studied, social isolation measurement, inflammation measurement, statistical analysis and study quality (see Table 3). Study heterogeneity was explored qualitatively and quantitatively with sensitivity analyses.

3.3.6. Populations studied

The majority of studies were conducted in the USA or Western Europe, with one additional study being conducted in a Taiwanese population (see Appendix VI). Most of the included papers sampled people from the community (see Table 3 and Appendix VI), with one additional study sampling from civil servants (A. Steptoe et al., 2003). The age of the included samples ranged from 20 or older (Ford et al., 2006) to 70–75 (Loucks et al., 2005, 2006a), with the majority of studies being conducted in people aged 35 or older (see Table 3 and Appendix VI).

Seven papers provided sex-stratified estimates (Ford et al., 2006; Haefner et al., 2011; Loucks et al., 2005, 2006a; Loucks et al., 2006b; Mezuk et al., 2010; Yang et al., 2013) with a further three being conducted in males only (Das, 2013; Helminen et al., 1997; Rosengren and Wilhelmsen, 1996). Where studies did provide sex-stratified estimates they more often found significant results for males. Of the six studies that provided sex-stratified estimates for CRP three found a significant association for males (Ford et al., 2006; Loucks et al., 2006a; Mezuk et al., 2010), with only one finding a significant association for females (Ford et al., 2006). Of the five papers that provided sex-stratified estimates for fibrinogen, four found a significant association in males (Loucks et al., 2005; Mezuk et al., 2010; Rosengren and Wilhelmsen, 1996; Yang et al., 2013), whereas only one found a significant association in females (Yang et al., 2013). Of the four studies that provided sex-stratified estimates for IL-6, two found significant associations in males (Loucks et al., 2006b; Mezuk et al., 2010) and one found a significant association in females (Loucks et al., 2006b).

Sensitivity analyses revealed that the majority of results were robust

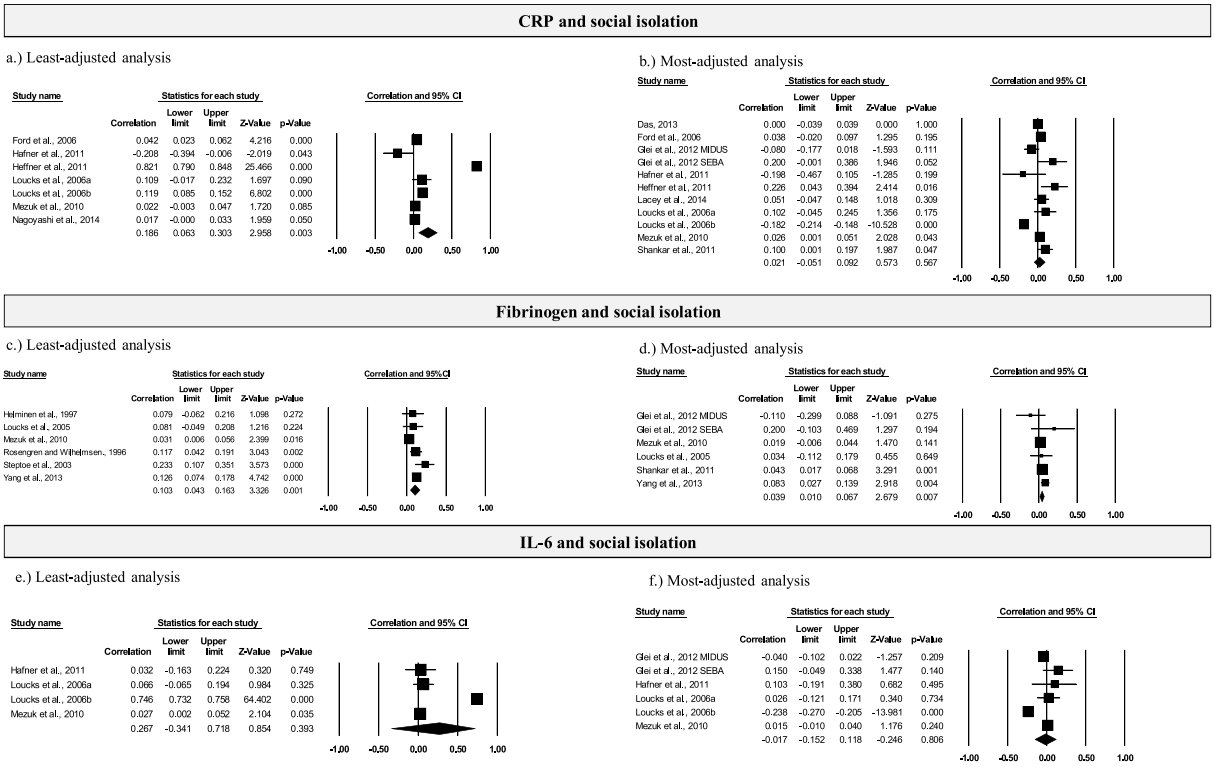

Fig. 3. Forest plots of association between social isolation with CRP, Fibrinogen and IL-6.

to stratification by different aspects of the population being studied (see Table 4). However, for the least-adjusted CRP and fibrinogen results sex stratification revealed that there was a significant association between these inflammatory markers with social isolation in males (CRP: r = 0.102, 95 % CI: 0.022, 0.180, p = .013; Fibrinogen: r = 0.117, 95 %CI: 0.047, 0.185, p = .001) but not females (CRP: r = 0.052, 95 %CI:-0.007, 0.111, p = .083; Fibrinogen: r = 0.041, 95 %CI:-0.016, 0.097, p = .160). The significant association for social isolation with these inflammatory markers for males was not seen in the most-adjusted analyses (see Table 4). Furthermore, the most-adjusted association between social isolation and fibrinogen became non-significant when only examining USA samples (r = 0.034, 95 %CI:-0.018, 0.086, p = .197) and when examining sex-stratified estimates (Males: r = 0.105, 95 %CI: -0.005, 0.212, p = .060; F: r = 0.015, 95 %CI: -0.038, 0.068, p = .585).

3.3.7. Social isolation measurement

Most included studies measured social isolation by measuring a person's social network (see Table 3 and Appendix VI). The most common measure was a derived social network index, normally based off the Berkman-Syme index (see Appendix VI), with most studies utilising a score of ≤ 1 to indicate social isolation (see Table 3). Other social network questionnaires included the Lubben social network index (Nagayoshi et al., 2014), the close person's questionnaire (A. Steptoe et al., 2003) and the social network component of the schedule for social interaction (Rosengren and Wilhelmsen, 1996). Two studies used social support questionnaires (Lacey et al., 2014; Briana Mezuk et al., 2010), and identified people with low social support.

Sensitivity analyses revealed that the association between social isolation and inflammation remained robust to the method of social isolation measurement, apart from one most-adjusted analysis (see Table 4). The overall most-adjusted effect for CRP was non-significant, however when social isolation was assessed with social support questions there was a significant association (r = 0.027, 95 %CI: 0.003, 0.052, p = .027)

3.3.8. Inflammation measurement

All included studies had a standardised protocol for assessing blood samples but differed in terms of venesection protocols (see Table 3). Eight papers mentioned a blood draw protocol that involved either having participants fast, having bloods taken at a specific time of and/or desisting from taking part in activities that could influence inflammation such as taking anti-inflammatory medication or drinking caffeine (see Appendix VI). In addition, only five studies excluded participants with high levels of inflammation prior to running their analyses, or controlled for factors known to influence inflammation (see Appendix VI).

Sensitivity analyses revealed that stratifying for different aspects of inflammation measurement did not affect estimates for IL-6 (see Table 4). However, the significant least-adjusted association between social isolation and CRP was only significant in those studies that did not account for high levels of inflammation (r = 0.259, 95 % CI: 0.041, 0.453, p = .020) or did not have a blood draw protocol that accounted for inflammatory confounders (r = 0.213, 95 % CI: 0.057, 0.358, p = .008). Where these inflammatory confounders were taken into account within the study design or analysis, there was not a significant unadjusted association (see Table 4). Finally, while the association between social isolation and fibrinogen remained mostly consistent, the fully-adjusted association in studies that accounted for high levels of inflammation became non-significant (r = 0.029, 95 % CI:-0.000, 0.059, p = .054).

3.3.9. Statistical analysis

Studies assessed the association between social isolation and inflammation using a range of statistical techniques (see Table 4) including linear regression, logistic regression and comparison of means (see Appendix VI). Of those studies that modelled inflammation as a continuous outcome, only five mentioned that they had checked for normality and when necessary, log-transformed their outcome or used non-parametric tests (see Appendix VI).

There was also heterogeneity for confounder control. Four studies

Table 4
Sensitivity analyses for associations of social isolation with CRP, fibrinogen and IL-6.

		CRP		Fibrinogen		IL-6	
		Least-adjusted*r* (95% CI)	Most-adjusted*r* (95% CI)	Least-adjusted*r* (95% CI)	Least-adjusted*r* (95% CI)	Least-adjusted*r* (95% CI)	Most-adjusted*r* (95% CI)
Population	Largest study removed	r = 0.208 (0.037, 0.037), p = .018	r = 0.020 (-0.060, 0.099), p = .627	r = 0.126 (0.089, 0.163), p < .001	r = 0.051 (0.013, 0.089), p = .008	r = 0.343 (-0.350, 0.793), p = .332	r=-0.025 (-0.177, 0.129), p = .775
	USA samples only	r = 0.233 (0.105, 0.353), P < .001	r = 0.002 (-0.084, 0.050), p = .961	r = 0.076 (0.000, 0.151), p = .049	r = 0.034 (-0.018, 0.086), p = .197	r = 0.339 (-0.362, 0.795), p = .345	r=-0.065 (-0.218, 0.092), p = .419
	Community samples only	All studies: r = 0.186 (0.063, 0.303), p = .003	All studies: r = 0.021 (-0.051, 0.092), p = .567	r = 0.084 (0.028, 0.140), p = .003	All studies: r = 0.039 (0.010, 0.067), p = .007	All studies: r = 0.267 (-0.341, 0.718), p = .393	All studies: r=-0.017 (-0.152, 0.118), p = .806
	Females only	r = 0.052 (-0.007, 0.111), p = .083	r=-0.063 (-0.188, 0.065), p = .334	r = 0.041 (-0.016, 0.097), p = .160	r = 0.015 (-0.038, 0.068), p = .585	r = 0.166 (-0.337, 0.596), p = .526	r = 0.124 (-0.152, 0.382), p = .378
	Males only	r = 0.102 (0.022, 0.180), p = .013	r = 0.009 (-0.059, 0.077), p = .798	r = 0.117 (0.047, 0.185), p = .001	r = 0.105 (-0.005, 0.212), p = .060	r = 0.171 (-0.071, 0.394), p = .164	r = 0.062 (-0.011, 0.136), p = .098
	People aged 50 or older	r = 0.119 (0.08, 0.149), p < .001	r = 0.034 (-0.084, 0.150), p = .577	r = 0.116 (0.077, 0.155), p < .001	r = 0.050 (0.027, 0.073), p < .001	r = 0.475 (-0.347, 0.884), p = .249	r=-0.035 (-0.283, 0.217), p = .787
Social isolation measurement	Social isolation measured with social network index	r = 0.231 (0.057, 0.358), p = .008	r = 0.025 (-0.093, 0.143), p = .678	r = 0.126 (0.089, 0.163), p < .001	r = 0.051 (0.013, 0.089), p = .008	r = 0.343 (-0.350, 0.793), p = .332	r =-0.025 (-0.177, 0.129), p = .755
	Social isolation measured with social support questions	N/A: Only Mezuk et al (2010)	r = 0.027 (0.003, 0.052), p = .027	N/A: Only Mezuk et al (2010)	N/A: Only Mezuk et al (2010)	N/A: Only Mezuk et al (2010)	N/A: Only Mezuk et al (2010)
Inflammation measurement	High levels inflammation/ people with inflammatory conditions or taking inflammatory medications accounted for: yes	N/A: Only Mezuk et al (2010)	r = 0.024 (-0.016, 0.065), p = .244	r = 0.032 (0.007, 0.057), p = .011	r = 0.029 (-0.000, 0.059), p = .054	N/A: Only Mezuk et al (2010)	r = 0.005 (-0.052, 0.062), p = .866
	High levels CRP /people with inflammatory conditions or taking inflammatory medications accounted for: no	All studies: r = 0.186 (0.063, 0.303), p = .003	r = 0.002 (-0.158, 0.161), p = .984	r = 0.130 (0.089, 0.171), p < .001	r = 0.077 (0.025, 0.129), p = .004	r = 0.343 (-0.350, 0.793), p = .332	r=-0.063 (-0.290, 0.170), p = .578
	Blood draw protocol that accounted for confounders: yes	r = 0.078 (-0.003, 0.158), p = .059	r=-0.004 (-0.134, 0.126), p = .949	r = 0.098 (0.026, 0.168), p = .007	r = 0.030 (0.006, 0.054), p = .014	r = 0.339 (-0.362, 0.795), P = .345	r=-0.031 (-0.173, 0.113), p = .675
	Blood draw protocol that accounted for confounders: no	r = 0.259 (0.041, 0.453), p = .020	r = 0.045 (-0.009, 0.099), p = .103	N/A: Only Yang et al (2013)	N/A: Only Yang et al (2013)	N/A: Only Haefner et al (2011)	N/A: Only Haefner et al (2011)
Statistical analyses	Linear analyses (linear predictor and outcome)	N/A: Only Haefner et al (2011)	r = 0.029 (-0.038, 0.095), p = .395	N/A	N/A: Only Shankar	N/A: Only Haefner et al (2011)	N/A: Only Haefner et al (2011)
	Categorical predictor, linear outcome	r = 0.311 (0.109, 0.488), p = .003	r=-0.027 (-0.172, 0.118), p = .713	r = 0.104 (0.018, 0.187), p = .017	r = 0.011 (-0.091, 0.113), p = .829	r = 0.458 (-0.399, 0.888), p = .290	r=-0.043 (-0.202, 0.119), p = .604
	Linear outcome normality accounted for: yes	N/A: Only Mezuk et al (2010)	r = 0.021 (-0.025, 0.068), p = .367	r = 0.066 (-0.018, 0.149), p = .121	r = 0.011 (-0.091, 0.113), p = .829	N/A: Only Mezuk et al (2010)	r = 0.005 (-0.052, 0.062), p = .866
	Linear outcome normality accounted for : no	r = 0.025 (-0.073, 0.123), p = .620	r=-0.098 (-0.281, 0.093), p = .316	r = 0.159 (0.005, 0.305), p = .042	N/A	N/A: Only Loucks, Sullivan et al (2006)	N/A: Only Loucks, Sullivan et al (2006)
	Categorical predictor (socially isolated versus not isolated)	r = 0.254 (0.115, 0.383), p < .001	r = 0.047 (-0.225, 0.312), p = .741	All studies: r = 0.098 (0.026, 0.168), p = .007	N/A	N/A	N/A
	Categorical analysis (socially isolated vs most integrated)	N/A: Only Loucks, Berkman et al (2006)	r = 0.050 (0.001, 0.098), p = .047	N/A: Only Yang	r = 0.077 (0.025, 0.129), p = .004	N/A: Only Loucks, Berkman et al (2006)	N/A: Only Loucks, Berkman et al (2006)
	All important confounders controlled for: yes	N/A	r = 0.001 (-0.107, 0.110), p = .979	N/A	r = 0.039 (-0.013, 0.091), p = .145	N/A	r=-0.031 (-0.173, 0.113), p = .675
	All important confounders controlled for: no	N/A	r = 0.053 (-0.027, 0.132), p = .195	N/A	N/A: Only Shankar et al (2011)	N/A	N/A: Only Haefner et al (2011)
Quality assessment: sensitivity	High quality studies	r = 0.119 (-0.026, 0.164), p = .151	r=-0.027 (-0.172, 0.118), p = .713	r = 0.066 (-0.018, 0.149), p = .121	r = 0.011 (-0.091, 0.113), p = .829	r = 0.458 (-0.399, 0.888), p = .290	r=-0.043 (-0.202, 0.119), p = .604
	Moderate quality studies	r = 0.230 (0.037, 0.408), p = .020	r = 0.050 (-0.001, 0.100), p = .055	r = 0.130 (0.076, 0.183), p < .001	r = 0.050 (0.027, 0.072), p < .001	r = 0.055 (-0.054, 0.163), p = .319	r = 0.041 (-0.091, 0.171), p = .544
	Low quality studies	N/A	N/A	N/A	N/A	N/A	N/A

N/A with no named studies indicates that there was no eligible data, and the sensitivity analysis could not be performed.
N/A with a named study indicates only the named study was eligible, and the sensitivity analysis could not be performed.

provided only unadjusted or minimally adjusted estimates. Where studies provided confounder-adjusted estimates seven controlled for all those important confounders identified for the quality assessment (Ford et al., 2006; Glei et al., 2012; Loucks et al., 2005, 2006a; Loucks et al., 2006b; Mezuk et al., 2010; Yang et al., 2013) and five controlled for some, but not all important confounders (see Appendix VI).

Sensitivity analyses indicated that the association between social isolation and IL-6 remained consistently non-significant (see Table 4). However, estimates for both CRP and fibrinogen were affected by different aspects of statistical analyses. For CRP, the significant least-adjusted estimate was reduced to non-significance for those studies that examined CRP as a linear outcome but had not accounted for the normality of their outcome (r = 0.066, 95 % CI: -0.018, 0.149, p = .121). Furthermore, there was a significant most-adjusted association for CRP when only examining those studies that compared the most socially isolated groups to the most integrated groups (r = 0.050, 95 % ci: 0.001, 0.098, p = .047).

The association between fibrinogen and social isolation was reduced to non-significance when examining only those studies that had accounted for data normality in linear analyses for both the least (r = 0.066, 95 % CI: -0.018, 0.149, p = .121) and most-adjusted (r = 0.011, 95 % CI:-0.091, 0.113, p = .829) analyses. In addition, those most-adjusted analyses where social isolation was assessed as a categorical predictor and fibrinogen as a continuous outcome (r = 0.011, 95 % CI: -0.091, 0.113, p = .829) and when studies accounted for the most important confounders (r = 0.039, 95 % CI:-0.013, 0.091, p = .145) were both reduced to non-significance.

3.3.10. Quality assessment

Only four studies were assessed as being high quality (Glei et al., 2012; Loucks et al., 2006b; Mezuk et al., 2010; Rosengren and Wilhelmsen, 1996), with all remaining studies having moderate quality (see Appendix II). The most common reasons for lowered quality assessment scores were having a protocol and/or analysis that did not account for high levels of inflammation, not accounting for all important confounders or not assessing social isolation with a validated questionnaire (see Appendix II).

When we conducted sensitivity analyses based on study quality, there was no effect on IL-6 estimates. However, the significant least-adjusted association between social isolation with CRP (r = 0.230, 95 % CI: 0.037, 0.408, p = .020) and fibrinogen (r = 0.130, 95 % CI: 0.076, 0.183, p < .001) was only observed in moderate quality studies (see Table 4). This pattern was also observed for the most-adjusted analysis between social isolation and fibrinogen (r = 0.050, 95 % CI: 0.027, 0.072, p < .001) (see Table 4).

4. Discussion

Results from this review indicate that there was an association between loneliness with the inflammatory cytokine IL-6 in adjusted analyses. Furthermore, there was a least-adjusted association between social isolation with the acute-phase proteins CRP and fibrinogen, and a most-adjusted association with fibrinogen. Our results also indicated that there was notable heterogeneity between studies both statistically and theoretically. Theoretical heterogeneity could be observed between studies for populations studied, statistical analyses, study quality and assessment of predictors and outcomes. When formally assessed with sensitivity analyses we found that sources of theoretical heterogeneity also impacted on some study results, leading to questions about the robustness of findings. A more detailed consideration of the link between loneliness with inflammation, and social isolation with inflammation is taken below.

4.1. Loneliness and inflammation

Previous narrative reviews have proposed that loneliness is linked with systemic inflammation (Eisenberger et al., 2017; Leschak and Eisenberger, 2019). We found a most-adjusted significant association between loneliness and IL-6. However, this result was based off two studies, one of which found a significant association (Nersesian et al., 2018) and one of which found a non-significant association (Hackett et al., 2012). As only two studies were synthesised we were unable to perform sensitivity analyses to determine the robustness of this association. Therefore, this result needs to be interpreted with caution. It is also worth noting that while the least-adjusted analysis was not significant, it did indicate a trend towards significance (p = 052). Taken in tandem, these findings indicate that more work on the association between loneliness and IL-6 is needed in order to draw any firm conclusions.

In addition we found that there was no overall association between loneliness with CRP or fibrinogen in either least-adjusted or most-adjusted analyses. However, when we examined sources of heterogeneity we did find that the age of the populations studied (being 50 or older), the location of the study (USA studies) and statistical analyses (linear analyses) led to some significant associations being uncovered in least-adjusted but not most-adjusted sensitivity analyses for CRP. Furthermore, we found that in most-adjusted analyses for fibrinogen that those studies that assessed loneliness with a single-item question and those where the protocol had not accounted for high levels of inflammation found significant associations between loneliness and fibrinogen.

The mixed results found for loneliness and inflammation could be because the relationship between loneliness and inflammation is not direct. The proposed pathway via which loneliness influences inflammation is through activation of the bodies stress system, including the sympathetic nervous system (SNS) and Hypothalamic Pituitary Adrenocortical (HPA) axis (Eisenberger and Cole, 2012; Eisenberger et al., 2017). Interestingly, experimental studies often do not find a direct relationship between loneliness and inflammation, but do find that the inflammatory response increases in reponse to manipulation of different stressors. For example, existing research shows us that lonely people have an increased inflammatory response in reaction to acute social stressors (Brown et al., 2018). Other studies show that people who are lonely have an enhanced immune response to biological challenges such as endotoxin (Jaremka et al., 2013) or vaccination (Balter et al., 2019). These findings suggest that loneliness could moderate how the immune system responds to biological and social stressors rather than having a direct impact on the immune system.

In considering how loneliness may be linked with inflammation there is also a need to consider the course of loneliness. For some people loneliness could be an acute state, and for others it could be chronic (Qualter et al., 2015). Theorists propose that acute and chronic psychosocial stressors have different effects on the inflammatory system (Hawkley et al., 2007). Acute stressors prime the immune system so that the body is prepared to react, so we typically oberve an association of acute stressors with upstream inflammatory markers such as interleukins (Marsland et al., 2017). However, chronic stress is proposed to be associated with dysregulation of the HPA-axis and higher levels of peripheral markers of systemic inflammation such as CRP (Hänsel et al., 2010). Interestingly recent longitudinal work from the English Longitudinal Study of Ageing suggested that a more chronic course of loneliness was associated with higher CRP in men (Vingeliene et al., 2019). Therefore, considering the chronicity of loneliness may be important for future work examining associations with inflammation. Furthermore, we need to bear in mind that reactions to loneliness may vary. For some people loneliness can be a transformative and overall positive experience as it acts as a motivator for them to reach out and develop new relationships (Moustakas, 2016). We suggest that future work is necessitated to understand whether the experience of loneliness as a chronic and/or stressful experience has a greater biological impact.

It is also possible that loneliness could be a consequence rather than antecedent of psychosocial stress. There are various studies showing

that those people who experience stressful major life events such as bereavements, experience chronic health conditions and are depressed could become lonely because of these stressors (J. T. Cacioppo et al., 2006; Dahlberg et al., 2015). All of these stressors share direct, independent associations with increased inflammation (Hänsel et al., 2010; Holwerda et al., 2014; Smith et al., 2018). It is, therefore, possible that loneliness itself does not cause inflammation, but it is risk factors for loneliness causing inflammation or that it is the interaction of loneliness with other social stressors that leads to activation of the immune system (Hawkley et al., 2007). There is a need for longitudinal studies to plot the relationship between psychosocial stressors, loneliness and inflammation over time to be better understand whether loneliness may be a moderator, rather than predictor of inflammation.

4.2. Social isolation and inflammation

Results from meta-analyses did not find any association between social isolation and IL-6, but they did find least-adjusted associations between social isolation with CRP and fibrinogen. Furthermore, we found that the association between social isolation and fibrinogen was also significant in most-adjusted analyses. However, we did find notable statistical and theoretical heterogeneity, which did impact on the robustness of estimates in some sensitivity analyses. The least-adjusted estimate between social isolation with CRP and fibrinogen was affected by different aspects of study heterogeneity, in particular, inflammation protocols and statistical analyses. Notably, significant associations were observed primarily in moderate quality studies that often did not account for important confounders, or inflammatory confounders within their study design or analysis. This indicates that the associations between social isolation and inflammation were found in studies that were less methodologically rigorous. However, in considering important confounders and methodological rigor it will be important for us as researchers to determine whether we want to 'control out' the effect of specific confounders to observe direct effects or whether it may be more important for us to examine potential intersections and interactions of different risk factors in predicting health outcomes in people who are socially isolated.

Social isolation has long being considered a potent social stressor which increases the risk of chronic illness and mortality (Cacioppo et al., 2015; Collaboration, 2010; Danesh et al., 1998). Social isolation is proposed to be particularly stressful because humans have evolved to be a social species, and when we don't have the contact with society that we need that this can have a direct impact on our biological, psychological and social wellbeing (Cruces et al., 2014). As noted in the discussion on loneliness, acute and chronic psychosocial stressors may have a differential impact on the inflammatory response. Interestingly, we observed an association between social isolation with downstream indicators of systemic inflammation (CRP and fibrinogen), suggesting that social isolation may be acting as a chronic stressor (Hänsel et al., 2010). However, more work is needed to understand the course of social isolation and how this might impact on inflammation.

As there is not a validated measure of social isolation we utilised a broad definition of social isolation as applied in previous research (Valtorta et al., 2016). This meant that many of the scales included were not designed to measure social isolation per se, instead they were designed to measure social networks and social support. Therefore, many studies were examining less socially integrated people rather than socially isolated people.

Sex-stratified sensitivity analyses revealed that the significant least-adjusted association between social isolation with CRP and fibrinogen was significant in males rather than females. However, it should be noted that of the sixteen included studies, only seven studies provided sex-stratified estimates and three were conducted in males only. It should also be noted that these were exploratory analyses. Despite this, we feel that these were interesting findings that could be explored more in future research. It is possible that sex differences could occur because males have increased activation of the HPA-axis in response to stress (Kudielka and Kirschbaum, 2005), which could, in turn, lead to greater inflammation (Black, 2002). Furthermore, research suggests that males and females exhibit different behavioural responses to social stress, with females being more likely to "tend-and-befriend" (i.e., seek out support) and males more likely to display a classic fight-or-flight stress response (Taylor et al., 2000). However, once confounders were taken into account there was no association between sex and inflammation. This suggests that rather than there being a direct relationship between social isolation and inflammation in males, that this might be explained by other factors. For example, the study of Haefner et al. (2011) found that social isolation did not have a significant association with inflammation. However, when they examined the interaction of social isolation with depression, they found that males had a greater inflammatory response. Therefore, further work investigating the role of confounders and effect modifiers may reveal interesting results with regards to the association of social isolation and inflammation in males.

4.3. Direction of causality

Only one study examining loneliness (Shiovitz-Ezra and Parag, 2018), and one study examining social isolation (Lacey et al., 2014) employed a longitudinal study design. The remaining studies were cross-sectional, meaning there are issues with inferring causality. Two recent papers not eligible for inclusion in this review as they used data utilised by Shankar et al. (2011) have modelled the longitudinal association between loneliness with inflammation (Vingeliene et al., 2019; Walker et al., 2019). Both employed different statistical methodologies, and one found that persistant loneliness was associated with higher CRP and fibrinogen in males (Vingeliene et al., 2019), whereas the other found that loneliness was not associated with CRP or fibrinogen but instead with markers of inflammation regulation (Walker et al., 2019). These differences in results using the same dataset highlight the impact that employing different statistical methodologies can have on results.

While our study modelled social isolation and loneliness as the predictors of inflammation it is plausible to assume that the opposite direction of causality could also explain findings. Previous research in the field of psychoneuroimmunology has posited the cytokine theory of depression, which suggests that depression is the result of a small yet significant increase in circulating inflammatory cytokines (Felger and Lotrich, 2013; Schiepers et al., 2005). Part of the support for the cytokine theory of depression comes from the fact that increases in cytokines cause a group of phenomenon termed 'sickness behaviours' which are similar to depression (Dantzer and Kelley, 2007; Schiepers et al., 2005). These symptoms include anhedonia, fatigue, sleep difficulties and mood dysregulation (Loftis et al., 2010). Interestingly another part of sickness behaviours includes socially isolating oneself, which could confer evolutionary advantage as those people who socially isolate themselves when ill are less likely to infect others (Moieni and Eisenberger, 2018). Furthermore, some researchers propose that inflammation may act to increase our sensitivity to social cues, and increase our desire to be around others to help with the healing process all of which could lead to increased feelings of loneliness (Eisenberger et al., 2017). It is, therefore, possible that inflammation could lead to social isolation and feelings of loneliness. This is supported by studies not eligible for inclusion in this review which show that when people are given an inflammatory challenge such as endotoxin or infected with the common cold that this often results people feeling significantly more socially disconnected or lonely than before the inflammatory challenge (Eisenberger and Cole, 2012; Eisenberger et al., 2010; Muscatell et al., 2016). This indicates that rather than loneliness and social isolation causing inflammation, that the opposite direction of association could be plausible and should be investigated in future work.

4.4. Strengths and limitations

This is the first systematic study to synthesise findings related to loneliness and social isolation with inflammation. However, some limitations with the review should also be noted. The inflammatory response is highly sensitive to influences beyond biological stressors such as viruses and physical illness, including adiposity (Elks and Francis, 2010), metabolic abnormalities (Sutherland et al., 2004), physical activity (Abramson and Vaccarino, 2002), mental illness (Bauer and Teixeira, 2019), older age (Baylis et al., 2013), psychological stress (Steptoe et al., 2007), smoking (Lee et al., 2012) and diet (Kiecolt-Glaser, 2010). However, few studies accounted for these within their statistical analysis or blood draw protocol. Furthermore, the use of anti-inflammatory medication would have a direct impact on levels of inflammation, but only seven studies accounted for this within their blood draw protocol (Hackett et al., 2012; Hasselmo et al., 2018; Helminen et al., 1997) or analysis (Glei et al., 2012; Mezuk et al., 2016; Mezuk et al., 2010; Shiovitz-Ezra and Parag, 2018). In future it will be important for studies to be more mindful of accounting for those confounders that can influence inflammation so that more reliable associations can be uncovered.

There was notable statistical and theoretical heterogeneity between studies, however these were explored qualitatively and quantitatively to assess the robustness of our findings. Broader issues with publication bias did not appear to be an issue with the review as many non-significant papers were found, though language bias may have been an issue as we only reviewed English language studies. Due to the nature of the studies included, it is possible that many socially isolated people would not have taken part, as recruiting socially isolated people would be difficult. Therefore, it is also possible that the results for social isolation may be underestimated.

Study generalisability could also be limited as many of the included studies were conducted in older adults limiting inferences to younger populations. Existing research suggests that loneliness and social isolation may affect health differently across the lifecourse (Hawkley and Capitanio, 2015) and researchers suggest that it is not until middle and older age that we are likely to observe an association between loneliness and isolation with physical health outcomes (Hawkley et al., 2007; Hawkley and Capitanio, 2015). However, we were not able to explore age-related differences due to the paucity of research in younger adults. This could represent an interesting avenue for future research. However, when looking at loneliness and social isolation with inflammation in older age it will be worth considering that older age in otherwise healthy individuals is also associated with increased low-grade inflammation, sometimes termed as 'inflammaging' (Baylis et al., 2013; Chung et al., 2011, 2009; Krabbe et al., 2004; Wolff et al., 2002). This could make uncovering associations more difficult, but it could also be interesting to examine the interaction of inflammaging with social stressors such as loneliness and social isolation.

Finally, we were limited in terms of the inflammatory markers that we could synthesise due to the small number of studies that examined markers other than CRP, fibrinogen and IL-6. More work is needed to ascertain whether other markers of inflammation may be linked with loneliness and social isolation. We also limited ourselves to markers of systemic inflammation. There is evidence showing that loneliness and social isolation are linked with the acute inflammatory response (Cruces et al., 2014; Kiecolt Glaser et al., 1984), and that loneliness alters the expression of genes involved in inflammation (Cole et al., 2007). Therefore, by only focusing on systemic inflammation we did not take into account other parts of the inflammatory system, which may also be associated with loneliness and social isolation.

4.5. Loneliness, social isolation and inflammation: do we need to think about the bigger picture?

The relationship between loneliness and social isolation with inflammation is likely much more complex than a simple direct relationship as we examined in this review. Loneliness and social isolation often co-occur with a wide range of individual (e.g., mental illness, chronic physical illness, major life events, lifestyle behaviours), social (e.g., living arrangements, discrimination, social networks) and structural (e.g., housing, poverty, neighbourhood characteristics) issues many of which are also risk factors for inflammation and poor health (Cohen-Mansfield et al., 2016; Hämmig, 2019; Mahon et al., 2006). This suggests that loneliness and social isolation should be considered as parts of a much bigger psychosocial picture of co-occurring issues that could all impact on inflammation (Egger et al., 2019). Rather than examine these risk factors singly, it will be important for future work to examine how different risk factors intersect and interact with both loneliness and social isolation in influencing health outcomes. Furthermore, by focusing only on inflammation we ignore the numerous related pathways (e.g., metabolic abnormalities, cardiac abnormalities, obesity) which can also be associated with loneliness and social isolation and also contribute to pathophysiological dysregulation and poorer long-term health (Cruces et al., 2014; Henriksen et al., 2019; O'Luanaigh et al., 2012; Xia and Li, 2018). Therefore, there is also a need for us to examine how inflammation intersects with other biological pathways that may link loneliness and social isolation to poorer health. By acknowledging the bigger picture in future work we will be able to better understand how and why loneliness and social isolation may affect health outcomes.

5. Conclusions

Results from this study provide some evidence that loneliness is linked with IL-6 and social isolation with CRP and fibrinogen. However, inferences are limited by the heterogeneity observed between studies and the fact that estimates were not robust to exploration of different sources of heterogeneity. In order to fully elucidate whether loneliness and social isolation are linked with inflammation there needs to be more consistency in methodology particular with regards to measurement, statistical analysis and accounting for important confounders. We also suggest that future studies might want to examine broader pathophysiological indicators beyond inflammation, and that consideration of the range of individual, social and structural issues linked with loneliness and social isolation may need to be taken into account.

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Declaration of Competing Interest

The authors declare that they have no competing interests

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.02.002.

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