

Social Support, Social Integration, and Inflammatory Cytokines: A Meta-Analysis

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Objective: Social support and social integration have been linked to lower rates of morbidity and mortality. However, the biological mechanisms responsible for such links need greater attention to advance theory and unique intervention opportunities. The main aim of this article was to conduct a meta-analytic review of the association between social support–social integration and inflammatory cytokines (e.g., interleukin-6, C-reactive protein) and test several proposed moderators from prior qualitative reviews. **Method:** A literature search was conducted using the ancestry approach and with databases PsycInfo, Medline, and EMBASE by crossing the exact keywords *social support* or *social integration* with *inflammation*. The review identified 41 studies with a total of 73,037 participants. **Results:** The omnibus meta-analysis showed that social support–social integration were significantly related to lower levels of inflammation ($Zr = -.073$). These results were not moderated by the operationalization of social relationships or the type of population, cytokine, and design. **Conclusions:** These data suggest that inflammation is at least one important biological mechanism linking social support and social integration to the development and course of disease. Future work should continue to build on this review and address next-generation questions regarding antecedent processes, mechanisms, and other potential moderators.

Keywords: social support, social networks, inflammation, cytokines, meta-analysis

Social relationships are a robust psychosocial predictor of physical health outcomes (House, Landis, & Umberson, 1988). In one meta-analysis, social support and social integration were associated with a 50% reduction in mortality rates, an effect size that was comparable to well-established lifestyle factors including smoking and physical activity (Holt-Lunstad, Smith, & Layton, 2010). The importance of social relationships for physical health sets the stage for work aimed at understanding mechanisms to facilitate theory and intervention development (Holt-Lunstad, Robles, & Sbarra, 2017; Taylor, 2010).

One important theoretical question pertains to the biological mechanisms underlying links between social relationships and health (Uchino, 2006). Understanding such mechanisms is important because it can advance theories that make more precise predictions about the links between social ties and specific disease outcomes based on the contributing physiology (Cohen, 2004). In addition, it could suggest novel interventions (e.g., behavioral and pharmacological) aimed at specific biological pathways. Given the important role that inflammatory cytokines play across diseases (Kiecolt-Glaser, Gouin, & Hantsoo, 2010), the major aim of this meta-analysis was to examine their association to measures of social support and social integration.

Inflammation and Health

There are a number of purported biological mechanisms linking social relationship to health (Uchino, 2006). Of these, inflammatory processes are likely to be key, given their influence across different diseases (Fagundes & Way, 2014). Inflammation is a normal defense reaction that plays a critical role in protecting the host from injury and infection. The local short-term inflammatory response (e.g., tissue injury) results in an influx of immune cells such as neutrophils–macrophages, the release of inflammatory cytokines, and changes in vascular permeability that allow the migration of immune cells to sites of injury. These processes serve critical functions by removing the source of injury–infection and promoting healing and tissue repair (Abbas, Lichtman, & Pillai, 2016). Many of these functions are initiated and regulated via the release of cytokines. Cytokines are proteins or glycoproteins, and the major inflammatory cytokines include interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF). C-reactive protein (CRP), which is an acute phase protein, is also often used as an indicator of inflammation (along with fibrinogen) because it rises dramatically in response to inflammatory stimulus. Although these cytokines are beneficial for short-term inflammation, long-term or chronic inflammation is detrimental (Hunter & Jones, 2015). For instance, immune-mediated inflammation can impact every stage of cardiovascular disease (Libby, Nahrendorf, & Swirski, 2016). At early stages of disease, IL-1 and TNF- α can increase the binding of low-density lipoprotein (LDL) to vessel walls, and up-regulate the LDL-receptor gene (Libby, Ridker, & Maseri, 2002). At later stages, IL-1 and TNF- α can increase the production of the protein metalloproteinase, which in turn can degrade the fibrotic cap of

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advanced lesions (Rajavashisth et al., 1999). Chronic inflammation is also present in the tumor microenvironment and appears to enable cancerous growth by promoting genetic instability and angiogenesis (Hanahan & Weinberg, 2011). In fact, chronic inflammation has been linked to a wide range of health problems, including diabetes, frailty, and overall mortality (Soysal et al., 2016, 2017; Wang et al., 2013).

Social Support, Social Integration, and Inflammation

Given that social relationships are linked to all-cause mortality, broad theoretical models highlight a potential link with inflammatory cytokines due to their established role across diverse diseases (Cohen, 2004; Uchino, 2006). More recent views have highlighted potential bidirectional links between social relationships and inflammation (Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017; Slavich & Irwin, 2014). According to social signal transduction theory, social threats can activate major brain regions associated with the release of inflammatory cytokines that become sensitized over time (Slavich & Irwin, 2014). Given that social support is a well-known buffer of stress reactions (Bowen et al., 2014; Cohen & Wills, 1985), it might decrease stress-induced inflammatory reactions. In addition, inflammation can influence relationship processes, as shown by research on sickness behavior (Eisenberger et al., 2017; Slavich & Irwin, 2014). Sickness-induced inflammation can directly lead to social withdrawal (A. H. Miller & Raison, 2016). Eisenberger and colleagues (2017) have recently proposed that inflammation can also increase sensitivity to positive social processes and foster effective support. By increasing one's sensitivity to positive social resources, individuals stand to benefit more from their relationships during times of need (Muscatell, Eisenberger, Dutcher, Cole, & Bower, 2016).

There have been several early qualitative reviews of this literature (Kiecolt-Glaser et al., 2010; Penwell & Larkin, 2010; Uchino, Vaughn, Carlisle, & Birmingham, 2012). In one of the first reviews, Kiecolt-Glaser and colleagues (2010) found that social support and social integration were related to lower IL-6 and CRP in several cross-sectional studies. Penwell and Larkin (2010) focused on 12 available studies and concluded that results were mixed and that it would therefore be premature to conclude that social relationships were linked to inflammation. Uchino and colleagues (2012) later suggested that there was preliminary evidence for social support and social integration's being related to lower IL-6 levels (e.g., Costanzo et al., 2005; Friedman et al., 2005), but this was the most commonly examined cytokine, although a few studies reported no link between social support and CRP levels (e.g., McDade, Hawkey, & Cacioppo, 2006). All of these reviews suggested important methodological issues (e.g., heterogeneous populations) and the need to link these data to theory on social relationships. Since these reviews, this literature has almost tripled and expanded on the types of cytokines included (e.g., TNF, fibrinogen). However, discrepancies are apparent in the recent literature because one study found that social support from family and friends was not associated with IL-6, TNF, or CRP levels (Nakata, Irie, & Takahashi, 2014), whereas another study found that friend support predicted a lower composite cytokine score (McHugh Power et al., 2016). Hence the use of meta-analytic techniques can better characterize the effect size linking social relationships to inflammatory cytokines and test its moderation via

several methodological and conceptual issues raised by prior reviews.

There are several important factors that might moderate the link between social relationships and cytokines. An important conceptual question relates to the different ways of measuring relationships, which have distinct theoretical implications (Cohen, 2004; Uchino, 2009). The classic review by Cohen and Wills (1985) made the distinction between structural and functional measures of support (also see Thoits, 2011). Social integration was viewed as a structural measure because it reflects the extent of one's social connections and access to support, often in important roles (e.g., marriage, friendships, volunteer organizations; Cohen, 2004). Although many interdisciplinary researchers have included social integration as an index of social support, these constructs have appeared separable on both empirical and conceptual grounds (Cohen, 2004; Holt-Lunstad et al., 2010; Uchino, 2004). Functional measures of support have included perceived and received support. Perceived support reflects the perception that support would be available if needed, whereas received support is the reported receipt of support during a particular time frame (Wills & Shinar, 2000). For instance, measures of perceived support often ask to what extent support would be available if needed, whereas received support might ask whether an individual received support during the past month. This distinction is significant because perceived support has been more consistently related to better health outcomes than has received support (Uchino, 2009; Wills & Shinar, 2000). In fact, received support often has variable links to health, because it might not be a good match to the needs of the recipient and can threaten a person's sense of independence (Bolger & Amarel, 2007).

There are also several important methodological issues that need consideration as moderators (Kiecolt-Glaser et al., 2010; Penwell & Larkin, 2010; Uchino et al., 2012). Given heterogeneity in the samples used, one important question relates to whether links are similar in studies utilizing relatively healthy individuals compared to studies focusing on chronic disease populations (e.g., cancer, cardiovascular disease). Models of social relationships and health highlight possible links to the development and/or course of chronic health conditions. That is, can social support influence the development of disease, or is it more influential once such chronic conditions arise and the need for support is high (Uchino, 2009)? If social support–integration and inflammation links are moderated by the type of population, then it would suggest stronger associations to particular phases of the disease process. A second important issue is related to whether the links are moderated by the type of cytokine. The most studied indicators of inflammation in terms of psychosocial processes are IL-6, TNF, fibrinogen, and CRP. Although early reviews were hampered by the fact that most studies examined IL-6, if this meta-analysis reveals evidence for specific cytokines it would highlight particular pathways of interest (Uchino et al., 2012). For instance, IL-6 is a pleiotropic cytokine that not only has inflammatory properties but also plays a role in T cell expansion and B cell differentiation (Hunter & Jones, 2015). Thus, if results were stronger for IL-6, then other mechanisms of influence would come into play. Such work could guide more specific models on biological mechanisms and guide the choice of cytokines in future theory testing. Finally, to address the potential directionality of the link between social support–integration with inflammation, we examined the type of design (i.e., cross-sectional, prospective) as a moderator.

The main aim of this review was thus to examine whether social integration and social support are linked to inflammatory cytokines, which might explain epidemiological links to disease outcomes. Qualitative reviews of this area have come to different conclusions and emphasized the need for greater work on the subject (Kiecolt-Glaser et al., 2010; Penwell & Larkin, 2010; Uchino et al., 2012). However, there does not appear to be any meta-analytic review of this literature despite its strong growth over the past 5 years. This meta-analysis thus documented the effect size of this association and tested several important moderators of such links based on prior theory and research.

Method

Identification and Inclusion–Exclusion of Studies

The review protocol used in this meta-analysis is detailed in this paragraph and the Analysis Plan and Data Extraction section. A literature search was first conducted using the major databases PsycInfo, Medline, and EMBASE by crossing the exact keywords *social support* or *social integration* with *inflammation*. This search was run up to February 2017 and identified 270 records, with 204 remaining after duplicates were removed (see Figure 1). Of these, 156 articles were rejected because they did not contain any quantitative data or did not include measures of social support or inflammatory cytokines. Of the remaining 48 records, seven were excluded for various methodological reasons, the most common being that no direct link between social support and inflammation was examined, given it was not a primary aim of the study. The ancestry approach was then used to search the reference list of all eligible articles and review articles on the topic (e.g., Penwell & Larkin, 2010). This resulted in a final count of 41 articles, with 47 independent effect sizes because several studies reported data from multiple, independent samples.

Analysis Plan and Data Extraction

Major details regarding studies (e.g., sample, type of support measure, outcomes) were first characterized and examined in tabular form. The subsequent meta-analysis was performed using a commercially available software package (MetaWin; Rosenberg, Adams, & Gurevitch, 2000) that provided results regarding effect sizes, confidence intervals, tests of variability regarding effect sizes, moderational analyses, and a fail-safe N . Fail-safe N represents the number of studies that would be required to overturn the conclusions of the meta-analysis due to missing or unpublished (i.e., file drawer) studies (Rosenthal, 1984). These analyses were based on a random effects model so that inferences could be made to studies on the topic more generally (Hedges & Vevea, 1998). To reduce the problem of nonindependence in omnibus analyses, when multiple assessments were reported (e.g., different cytokines, support measures) we first transformed them to a common metric which were then averaged and entered into the meta-analysis. Correlation coefficients (r) were used as the common metric for data entry. When correlations were not presented, measures of effect size were converted to r values. Odds ratios were transformed based on the formula $r = (\text{OR}^{[3/4]} - 1) / (\text{OR}^{[3/4]} + 1)$ by Bonett (2007), and when multiple contrasts were reported, the difference between the low and high categories was extracted. Standardized regression weights were converted using the formula $r = \beta + .05\lambda$ (Peterson & Brown, 2005). When p values were the only source of data, they were transformed using the equation $r = z/\sqrt{N}$ based on the one-tailed z score. Results reported as nonsignificant utilized a conservative significance level of .50 (Rosenthal, 1984). Publication bias for the omnibus meta-analysis was done at the outcome level by calculating a funnel plot, Kendall's tau, and the fail-safe N . Finally, metaregressions were done based on the earlier qualitative reviews and examined support measure, type of population, outcome, and study design.

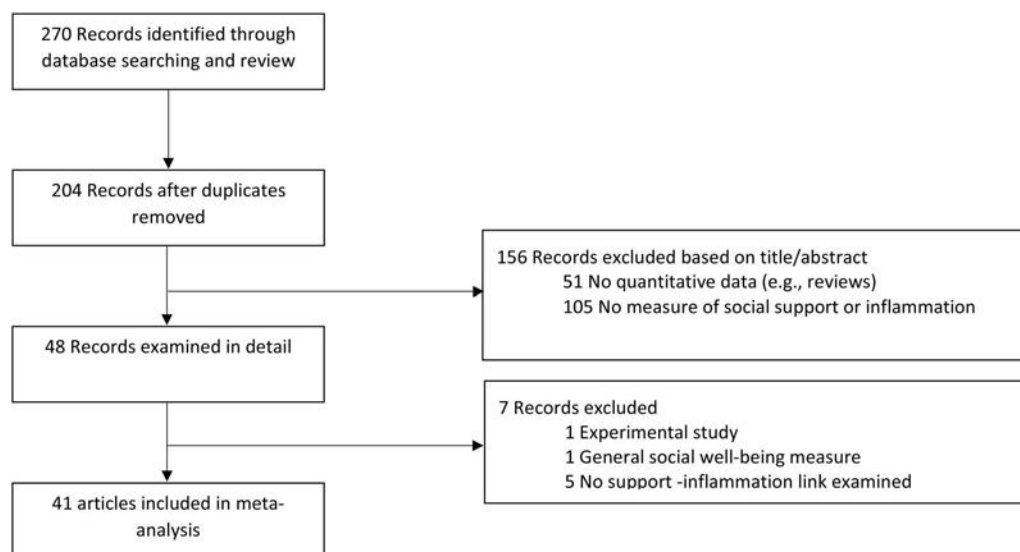


Figure 1. Flowchart describing exclusion and inclusion details for studies in the meta-analysis.

Results

Overview of Studies

The main characteristics of these studies are shown in Table 1. At least two authors verified the accuracy of the details listed in the table that was subsequently also used in the moderator analyses. In

total, 73,037 participants were included in the meta-analysis. Most of these studies utilized relatively healthy samples (79%) as opposed to samples with chronic conditions (e.g., cancer). The most common support measure examined across studies was perceived support (55%), followed by social integration (49%) and received support (15%). In terms of inflammatory cytokines, the most

Table 1

Methodological Details and Outcomes For Each Study Used in The Meta-Analysis

Study	N ^a	Analyses	Sample	Support measure	Main inflammatory markers	Effect size (Zr) ^b	Var (Zr)
Davis & Swan (1999)							
Study 1	46	CS	NC	RSS	Fibrinogen	.030	.023
Study 2	42	CS	NC	RSS	Fibrinogen	-.343	.020
Lutendorf et al. (2000)	54	CS	NC, C	RSS	IL-6	-.343	.017
Hemingway et al. (2003)	283	CS	NC	RSS	CRP, IL-6	.000	.004
Marucha et al. (2005)	44	P	C	SI	Stimulated TNF	.377	.024
Loucks et al. (2005)	399	CS	NC	SI	Fibrinogen	-.121	.003
Costanzo et al. (2005)	36	CS	C	PSS	IL-6	-.050	.017
McDade et al. (2006)	188	CS	NC	PSS	CRP	.000	.005
Loucks, Sullivan, Berkman, et al. (2006)	3,127	CS	NC	SI	CRP, IL-6	-.050	.000
Loucks, Berkman, et al. (2006)	402	CS	NC	SI	CRP, IL-6	-.121	.002
Ford et al. (2006)	14,818	CS	NC	SI	CRP	-.025	.000
Von Ah et al. (2007)	54	CS	C	PSS	Stimulated INF-gamma	.141	.020
Marsland et al. (2007)	177	CS	NC	PSS, SI	Stimulated IL-8, IL-6, IL-1, TNF	-.161	.006
Coussons-Read et al. (2007)	52	CS	NC	PSS	IL-6, IL-10, TNF, CRP	-.030	.020
Kamiya et al. (2010)	5,884	CS	NC	PSS, SI	CRP, fibrinogen	-.020	.000
Mezuk et al. (2010)	3,460	CS	NC	PSS	IL-6, CRP, fibrinogen	-.182	.000
Shankar et al. (2011)	5,437	CS	NC	SI	CRP, fibrinogen	-.090	.000
Heffner et al. (2011)	370	CS	NC	SI	CRP	-.321	.000
Glei et al. (2012)							
Study 1	970	CS	NC	SI, PSS	CRP, fibrinogen, IL-6	.03	.001
Study 2	961	CS	NC	SI, PSS	CRP, fibrinogen, IL-6	-.01	.001
Chiang et al. (2012)	121	CS	NC	PSS/RSS	IL-6	-.172	.009
Nakata et al. (2014)	137	CS	NC	PSS	IL-6, TNF, CRP	-.060	.008
Yang et al. (2014)	647	P	NC	PSS	IL-6, fibrinogen, CRP	-.100	.002
Shimano et al. (2014)	7,873	CS	NC	RSS	CRP	-.030	.000
Kreibig et al. (2014)	1,019	CS	C	SI	CRP	-.100	.001
Seeman et al. (2014)	782	CS	NC	PSS, SI	IL-6, CRP composite	-.085	.001
Runsten et al. (2014)	116	CS	NC	PSS	CRP	-.192	.009
Hughes et al. (2014)	164	P	C	PSS	IL-6	-.224	.006
Yang et al. (2014)	1,075	CS	C	SI	CRP, fibrinogen	-.070	.001
Copertaro et al. (2014)	232	CS	NC	PSS	TNF	-.277	.004
Giurgescu et al. (2015)	49	CS	C	PSS	IL-1, IL-2, IL-6, IL-8, IL-10, TNF, INF	-.141	.022
Nowakowski & Sumerau (2015)	803	CS	NC	PSS	CRP	-.045	.001
Tomfohr et al. (2015)	67	CS	C	PSS	IL-6, CRP, TNF	.04	.016
Cho et al. (2015)	2,962	P	NC	SI	CRP, IL-6	-.043	.000
Gouin et al. (2016)	44	CS	NC	PSS	CRP	-.141	.024
Eguchi et al. (2016)	2,020	P	NC	PSS	CRP	-.040	.001
Guan et al. (2016)	316	CS	NC	RSS	CRP	.045	.003
Uchino et al. (2016)	281	CS	NC	PSS	CRP	.070	.004
Bajaj et al. (2016)							
Study 1	306	CS	NC	PSS, SI	CRP, IL-6	.030	.003
Study 2	419	CS	NC	PSS, SI	CRP, IL-6	.010	.002
Muscatell et al. (2016)	30	CS	NC, C	PSS	IL-6, CRP	-.315	.037
Yang et al. (2016)							
Study 1	6,747	P	NC	SI	CRP	-.105	.000
Study 2	863	P	NC	SI	CRP	.010	.001
Study 3	4,323	P	NC	SI	CRP	-.060	.000
Study 4	1,153	P	NC	SI	CRP	-.203	.001
Kim et al. (2016)	3,568	CS	NC	SI	Fibrinogen	-.141	.003
Power et al. (2016)	116	CS	NC	SI, PSS composite	Chemokine, cytokine composite	.027	.009

Note. Var = variance; CS = cross-sectional; P = prospective; NC = nonclinical; C = clinical; PSS = perceived social support; RSS = received social support; SI = social integration; IL = interleukin; TNF = tumor necrosis factor; INF = interferon; CRP = C-reactive protein; N=sample size.

^a The average sample size is reported for studies with multiple measures of support or inflammatory cytokines. ^b Fisher's transformation of *r*.

common measures were CRP (70%), IL-6 (45%), fibrinogen (23%), and TNF (15%). Most studies examined cytokines in the peripheral circulation (94%) in comparison to cytokines produced in vitro during stimulation.

What Is the Overall Link Between Social Support, Social Integration, and Inflammation?

Across all 47 studies, the weighted random effect size was significant ($Zr = -.073$, 95% confidence interval $[-.10, -.05]$, $p < .05$) and showed that social support and social integration were related to lower levels of inflammatory cytokines. Effect sizes ranged from $Zr = -.34$ to $Zr = +.38$, and the test of heterogeneity was significant: $Q_{(46)} = 68.6$, $p = .02$. To examine the possibility of bias, we plotted a funnel plot of effect sizes as a function of sample size. Smaller samples should produce more heterogeneity in effect sizes, resulting in a roughly symmetric funnel plot that gets smaller with increasing samples sizes (Rosenberg et al., 2000). As shown in Figure 2, this pattern was obtained. A direct test of the association between effect sizes and sample sizes revealed a nonsignificant link (Kendall's $\tau = .083$, $p = .41$), again suggesting a lack of publication bias. Finally, we calculated the fail-safe N , which is the number of studies with no effect ($r = 0$) that would be required to render the omnibus test nonsignificant (Rosenthal, 1984). The resulting fail-safe N was 639.7, which is larger than the general guideline of $5k + 10$, where k is equal to the number of studies in the meta-analysis.

What Are the Moderators of Links Between Social Support, Social Integration, and Inflammation?

The significant test of variability suggests potential moderators of the link between social support–social integration and inflammatory cytokines. As a result, moderator analyses were run to test issues raised by prior qualitative reviews and begin to characterize

Table 2

Main Results of Meta-Regressions Testing Moderators of The Social Support-Inflammation Link

Moderator	<i>k</i>	Effect size (<i>Zr</i>)	95% CI
Support measure			
Social integration	22	-.076	$[-.11, -.04]$
Perceived support	24	-.054	$[-.09, -.02]$
Received support	6	-.040	$[-.14, .06]$
Sample			
Clinical	10	-.082	$[-.16, -.003]$
Nonclinical	39	-.071	$[-.10, -.047]$
Cytokine			
Fibrinogen	11	-.072	$[-.12, -.02]$
IL-6	20	-.078	$[-.12, -.03]$
CRP	32	-.064	$[-.09, -.04]$
TNF	7	-.076	$[-.19, .04]$
Design			
Cross-sectional	38	-.077	$[-.11, -.05]$
Prospective	9	-.062	$[-.11, -.01]$

Note. k = number of studies; Zr = Fisher's transformation of r ; CI = confidence interval; IL = interleukin; CRP = C-reactive protein; TNF = tumor necrosis factor.

the resulting effect sizes. One of the more important issues is whether the link varies by how these relationship variables are operationalized. That is, do measures of social integration, perceived support, and received support have similar effect sizes, given they are separable dimensions of relationships with distinct links to health? As shown in Table 2, these analyses revealed that the effect size was largest for measures of social integration ($Zr = -.076$), followed by perceived ($Zr = -.054$) and received ($Zr = -.040$) support. However, the test of differences in effect sizes as a function of the type of support measure was not significant: $Q_{(2)} = 1.35$, $p = .61$.

It is also possible that effect sizes might differ based on whether the sample has a chronic condition in which social support is

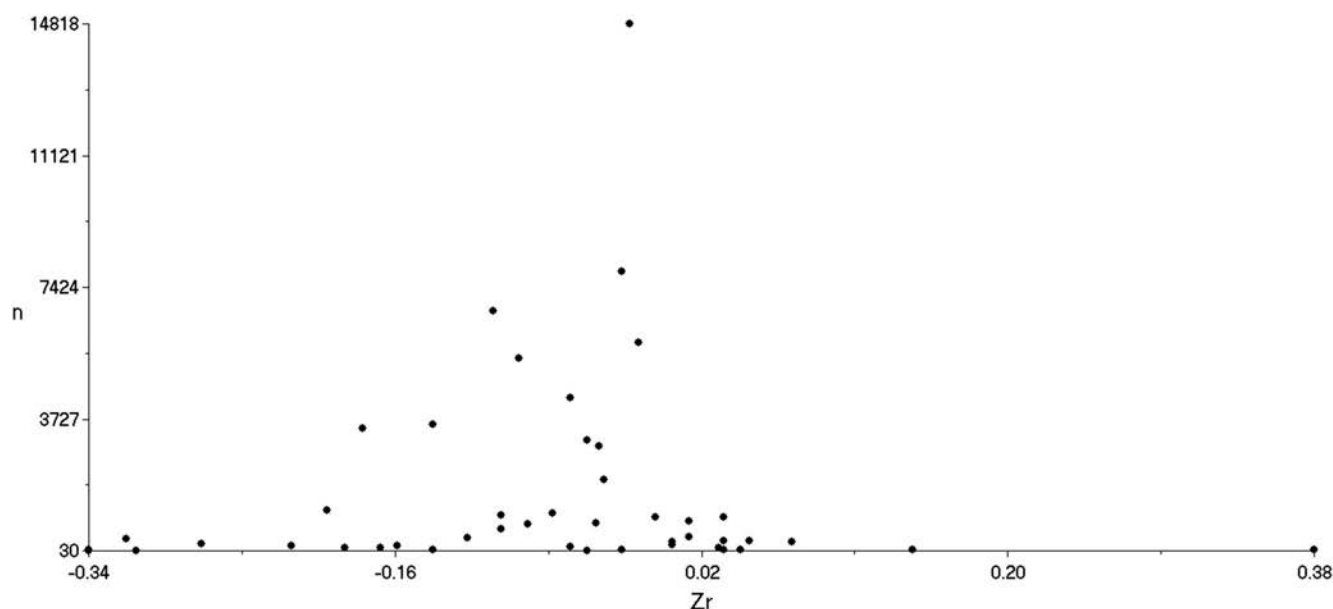


Figure 2. Funnel plot depicting the association between effect (Zr) and sample sizes (n).

particularly impactful (Berg & Upchurch, 2007). Ten studies explicitly used a clinical sample, most often cancer patients, but these studies produced similar effect sizes compared to nonclinical samples ($Z_{rs} = -.082$ vs. $-.071$, respectively), $Q_{(1)} = .08$, $p = .80$ (see Table 2). The type of cytokine was examined because some cytokines have broader influences on disease-relevant pathways (e.g., IL-6) and there is a larger epidemiological literature linking some of these to health (e.g., CRP). Only cytokines that had at least five effect sizes (i.e., CRP, IL-6, fibrinogen, TNF) were included so we could more reliably characterize potential effect sizes. As shown in Table 2, results of these moderator analyses showed that effect sizes were comparable and not significantly different based on the categorical analysis: $Q_{(3)} = .36$, $p = .95$. Finally, moderator analysis examined whether the type of design (i.e., prospective or cross-sectional) influenced effect sizes. No differences emerged, however, between prospective and cross-sectional studies: $Q_{(1)} = .33$, $p = .63$.

Discussion

The main goal of this review was to examine the meta-analytic link between social support, social integration, and inflammation, as well as test several important moderators of such associations. Results of omnibus analyses revealed that social support–integration were significant predictors of lower inflammation, with little evidence for bias in the review. In addition, these results were comparable across the different measures of relationships, populations, inflammatory markers, and study design. These findings are important because they suggest that inflammation is at least one important biological pathway linking positive social relationships to lower risk for the development and clinical course of health problems (e.g., cardiovascular disease; Hunter & Jones, 2015; Libby et al., 2016). However, the number of studies in subcategories of these moderator analyses was relatively small, so more work will be needed to definitively address more complex associations. In addition, there is always a risk of publication bias in meta-analytic reviews.

The potential moderation as a function of the relationship measure requires particular attention, given theoretical arguments in prior reviews (Cohen, 2004; Uchino, 2009). It has been argued that received support is contextual and hence its influence on outcomes might be more variable (Bolger & Amarel, 2007; Uchino, 2009). Inconsistent with this possibility, the effect size estimates were not significantly different based on the moderator analyses. There are several potential explanations for such findings. First, it is possible that individuals were receiving responsive support (i.e., support that is viewed as validating and caring in nature; Reis, 2007), which is more likely to be beneficial (Selcuk & Ong, 2013). No study, however, directly assessed this possibility, so future work should include responsiveness to aid in future reviews of this issue. Second, there were only six studies that examined received support, so perhaps more studies are needed to produce a reliable estimate because only one of the received support studies utilized a large sample size (Shimano et al., 2014). Indeed, the confidence interval linking received support and inflammation included zero (indicating a nonsignificant link as well as) the possibility of a detrimental influence. As a result, strong conclusions of the role of received support will require

more studies that also measure theoretically important contextual factors.

It was also the case that the effect size for social integration was the largest of the three major measures. This is consistent with the Holt-Lunstad et al. (2010) meta-analysis in which more complex measures of social integration, compared to perceived and received support, appeared to have stronger links to all-cause mortality. There are several potential reasons why social integration might be associated with larger effect sizes. First, social integration measures are perhaps the broadest, given it assesses important social roles (e.g., marriage, volunteer organizations) and hence may be tapping into more health-relevant processes, including social support (Uchino, 2004). That is, social integration has been argued to operate primarily as a main effect independent of stress levels (Cohen, 2004; Cohen & Wills, 1985). As a result, it can influence broader and more pervasive everyday situations such as social control, a sense of identity, self-worth, and positive affect, which are beneficial to health (Cohen, 2004). Some researchers have also argued that social integration may have stress-buffering properties, hence expanding the set of processes linking it to health (Barrera, 1986; Uchino, 2004).

The moderator analysis also did not show any differences as a function of the type of cytokine. In these analyses, the individual effect sizes for the major cytokines (i.e., CRP, IL-6, fibrinogen) were significant with the exception of TNF. However, this review examined only a subset of cytokines and inflammatory markers. This is important because the balance of proinflammatory and anti-inflammatory cytokines appears critical for both cardiovascular disorders and cancer progression (Hanahan & Weinberg, 2011; Libby et al., 2016). Only two studies in this review examined anti-inflammatory processes (Coussons-Read, Okun, & Nettles, 2007; Giurgescu et al., 2015), and both found no association with social support–social integration, although the samples sizes were small ($Ns < 53$). More work is also needed on immune cells that are major contributors to cytokine release. Such work can help researchers better understand how the migration of these cells influences both local and systemic inflammatory responses (Libby et al., 2016). In fact, different cell subtypes appear to be critical to the beneficial versus detrimental influence of cytokines on diseases such as cancer (Hanahan & Weinberg, 2011). Finally, potential links between social relationships and genetics (e.g., gene expression), especially inflammatory genes, might also prove fruitful to understand its origins.

It is also worth noting that the omnibus effect size linking positive aspects of social relationships to inflammation was small ($Z_r = -.073$). This small effect size is consistent with results in a recent meta-analysis examining marital quality and measures of peripheral physiology (Robles, Slatcher, Trombello, & McGinn, 2014). Given that inflammation is simply one pathway possibly linking social relationships to health and is itself a multiply determined measure, the effect size is not entirely unexpected. In addition, the complexity of inflammatory processes may result in lower effect sizes due to unmeasured biological influences that vary over time. For instance, inflammation is likely a more downstream physiological pathway because it is activated by both the autonomic and endocrine systems (Soszynski, Kozak, Conn, Rudolph, & Kluger, 1996). Glucocorticoids in the short-term can also decrease inflammation but, under conditions of chronic stress, can lead to gluco-

corticoid resistance, in which the inflammatory response bypasses this important control mechanism (G. E. Miller, Cohen, & Ritchey, 2002). Thus, future work that models the complex biological sequelae associated with inflammation will be important for theoretical development.

Moderator analyses of cross-sectional and prospective studies did not show differential associations between social relationships and inflammation. These results suggest that social support and social integration appear to influence inflammatory cytokine levels. Nevertheless, it is likely that such links are bidirectional over time. Inducing inflammation is known to increase social withdrawal as part of the constellation known as sickness behavior (A. H. Miller & Raison, 2016). However, it has been recently proposed that the link between inflammation and social processes is contextual and can also increase sensitivity to positive support exchanges in close relationships (Eisenberger et al., 2017). Such transactions over time may increase perceptions of support and trust in close relationships, which in turn reduce stress-induced inflammation. Stress and sickness-induced inflammation may also play a role in the development of depression (Slavich & Irwin, 2014), which can lead to an erosion of support over time (Bolger, Foster, Vinokur, & Ng, 1996) that further exacerbates inflammation (Slavich & Irwin, 2014). Prospective and daily diary studies can best capture how fluctuations in relationships and inflammation influence each other over time.

In summary, this review advances the literature in demonstrating that inflammation is at least one important biological pathway linking social support and social integration to health. Future work should examine next-generation questions that help explain more of the variance, including specific precursors of support (e.g., early family environment), support moderation via important personality and experiential factors, and bidirectional pathways (Taylor, 2010). In addition, most of the studies in this meta-analysis utilized general measures of support. In comparison, specific functional assessments of support (e.g., emotional support, tangible support) should be utilized because they provide greater guidance for translational work. The future work made salient by this meta-analytic review will allow for the building of complex models that can guide intervention work and make salient multiple entry points for intervention (e.g., social, biological).

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