

Higher interleukin-6 is associated with greater momentary social connection in close relationships in daily life

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ARTICLE INFO

Keywords:

Inflammation
Interleukin-6
Close relationships
Social approach
Social connection

ABSTRACT

Recent evidence has documented associations between higher levels of inflammation and social approach behaviors toward close others in laboratory-based tasks. Yet it is unknown if this translates to interactions with close others in daily life. Given that momentary experiences of social connection have both relational and health consequences, this is a critical gap in our knowledge. To address the association between inflammation and momentary social connection experiences in close relationships, 55 participants provided blood samples on two consecutive days, which were assayed for circulating levels of the inflammatory marker interleukin-6 (IL-6). After providing the first blood sample, participants received the annual influenza vaccine as a mild inflammatory challenge. Participants also reported on cognitive, affective, and behavioral indicators of social connection with a specific close other multiple times across the two study days. Results indicated that levels of IL-6 were positively associated with temporally-proximal indicators of momentary social connection with a close other. Specifically, higher levels of IL-6 were associated with greater feelings of comfort from the close other, greater desire to be near them, and higher reported relationship quality. Greater IL-6 reactivity to the vaccine was only associated with increased reported relationship quality. These data add to the existing literature suggesting that higher levels of IL-6 may motivate social approach toward a close other, extending evidence to now include momentary social connection experiences in daily life.

1. Introduction

Accumulating research suggests that inflammation is associated with social approach behavior toward those we feel close to (Eisenberger et al., 2017; Hennessy et al., 2014). This may be partly due to the fact that it is evolutionarily-adaptive to approach “close others” when experiencing high levels of inflammation, as close others can provide comfort and care to help with recovery and survival (Muscatell and Inagaki, 2021). To date, evidence that inflammation is related to social approach behavior in humans comes primarily from studies using neuroimaging (e.g., greater neural activity in the ventral striatum to images of support figures, Inagaki et al., 2015) or computer-based measures of approach behavior (e.g., faster reaction times approaching images of a support figure, Jolink et al., 2022). Outside the lab, heightened

inflammation has been linked with a curbing of peripheral social network ties yet the maintenance or creation of close ties (e.g., in women caring for a child with cancer, Lindsay et al., 2022; among college students forming a social network, Kornienko et al., 2022). Taken together, this work suggests that higher inflammation may be associated with greater motivation to approach and solidify bonds with close others.

Despite this recent evidence that inflammation is associated with social approach toward close others, very limited work has examined associations between inflammation, specifically, the inflammatory cytokine interleukin-6 (IL-6), and *momentary* thoughts, feelings, and behaviors in close relationships that promote social connection. This presents a critical knowledge gap, for two primary reasons. First, proximal (e.g., daily) experiences of social connection in close relationships predict important outcomes, including higher daily relationship and life

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satisfaction (Cameron and Overall, 2018; Chang et al., 2022), healthy cortisol profiles (Ditzen et al., 2008; Slatcher et al., 2010), better sleep quality (Kane et al., 2014), fewer somatic symptoms (Stadler et al., 2012), and lower perceived stress (Shrout et al., 2020). Second, inflammation is linked with other daily or momentary experiences (for review, see Jones and Graham-Engeland, 2021), such as increases in depressed mood (Kuhlman et al., 2018) and decreases in positive affect in response to daily stressors (Sin et al., 2015). Thus, we sought to examine whether inflammation (i.e., IL-6) was associated with a novel type of momentary experience that is predictive of important outcomes: indicators of social connection toward a close other.

The prior known studies that have examined peripheral inflammation and proximal experiences of social connection have yielded mixed results. In one study using ecological momentary assessments (EMAs), more frequent positive interactions with close others were associated with lower IL-6 (Bajaj et al., 2016). “Positive interactions” in this study were operationalized as the self-reported frequency of positive/pleasant interactions, which, while informative, does not provide detail about what may have occurred during the interactions that made them positive. Another study also examined interaction frequency and concurrent inflammation, both measured three times at two-week intervals over one month (Jolink et al., 2023). This study found that spending more time co-present with a romantic partner in 24-h was associated with lower CRP but once again *how* one specifically spent this shared time with their partner was not examined. Finally, in a third study, changes in IL-6 in response to influenza vaccine were not associated with changes in daily social connection across a 14-day diary (Kuhlman et al., 2018), though the social connection measure used did not ask about a specific close other and instead measured broad feelings of social connection. Altogether, some prior work has shown an association between inflammation levels—measured in a variety of ways—and frequency of interactions with close others. However, there remain gaps in our knowledge regarding what is happening—real or imagined—during those interactions. How is inflammation associated with the specific and momentary ways we connect with friends and romantic partners? The answer to this will inform when and why we might expect certain relational processes to be associated with heightened inflammation, but others associated with lower inflammation. The present study addresses this question by measuring multiple thoughts, feelings, and behaviors related to momentary social connection with a close other and their associations with inflammation.

Prior work has also found links between momentary psychological measures and physiological responses (e.g., momentary stress and cardiovascular measures, Kamarck et al., 2005; momentary positive affect and post-stressor diastolic blood pressure recovery, Steptoe et al., 2007). On inflammation specifically, momentary assessment methods have documented negative associations between inflammation and momentary positive affect and positive associations between inflammation and momentary negative affect (Graham-Engeland et al., 2018, 2022; Jones et al., 2020; Steptoe et al., 2008). In the present study, we were interested in expanding the conversation about inflammation and momentary psychosocial experiences to include social connection with a close other.

To examine associations between IL-6 and momentary social connection with a specific close other, we used eight repeated momentary reports to measure a constellation of social connection experiences with a friend, roommate, or romantic partner before and after receipt of the annual influenza vaccine. Momentary measures of social connection occurred before and after two blood collections (one before and one after the vaccine) from which IL-6 was assayed. We investigated the association between momentary social connection experiences with a close other and both IL-6 reactivity to the vaccine (i.e., change in IL-6 from pre- to post-vaccine) and levels of IL-6 (i.e., IL-6 levels in both blood samples).

IL-6 was selected as the inflammatory cytokine of interest in this study for a few reasons. First, changes in the inflammatory cytokine IL-6

in response to vaccines have been linked with corresponding behavioral and neural changes in humans (e.g., endotoxin, DellaGioia and Hanestad, 2010; Inagaki et al., 2012; influenza; Kuhlman et al., 2018; Jolink et al., 2022; typhoid, Lacourt et al., 2015; Madison et al., 2023; Wright et al., 2005). Next, research mapping the time course of the inflammatory response to the influenza vaccine has found evidence that IL-6 is often significantly increased approximately 24-h after vaccine injection (Christian et al., 2013; Tsai et al., 2005); Radin et al. (2021) found IL-6 levels peaked for the majority of participants 24-h post-vaccine. To our knowledge, the time course of inflammatory reactivity to the influenza vaccine is currently unknown for other cytokines. Finally, other studies using the influenza vaccine as a mild inflammatory challenge have focused on IL-6 as the immune marker of interest (Carty et al., 2006; Christian et al., 2011; Edwards et al., 2006; Segerstrom et al., 2012; Tsai et al., 2005). To keep our study in conversation with the existing literature, we also focused on IL-6 as the target inflammatory cytokine.

2. Materials and methods

2.1. Participants

Fifty-five healthy young adults (37 identified as biologically female; mean age=20.06 years, $SD=1.34$) from UNC-Chapel Hill in Chapel Hill, North Carolina, USA were recruited to participate in a study in spring 2022 (until the influenza vaccine was no longer available at the campus pharmacy).³ Participants were part of a larger study investigating associations between inflammatory reactivity to the influenza vaccine and psychosocial processes. Participants self-identified their race/ethnicity and were able to choose multiple identities: 28 identified as White/Caucasian (51%), 18 identified as Asian/Asian American (33%); 10 identified as Latina/(o) Chicana/(o) Latin American (18%); 5 identified as Black/African American (6%); 2 identified as Native American (4%); and 2 identified as Middle Eastern (4%).⁴ Participants were eligible if they were between ages 18–25 and had a non-familial close other in their lives whom they saw daily. Participants were included regardless of hormonal contraceptive use and menstrual phase (i.e., we did not restrict our sample based on the use of contraceptives, nor did we schedule participants around menstrual cycle phase). Participants who identified as biologically female responded to one question about their contraceptive use: 21 participants reported not using any birth control, with the remaining participants reporting using hormonal IUDs ($n=3$), implants ($n=2$), oral contraceptives ($n=9$), a fertility-awareness method ($n=1$), or were missing data ($n=1$). Participants were ineligible if they had already received the influenza vaccine or had the flu that season, had current or a history of depression, anxiety, or any major medical condition (e.g., diabetes, asthma), had Guillain-Barre Syndrome, used tobacco products, were allergic to eggs or ingredients present in the vaccine, had ever had an adverse reaction when providing a blood sample, or were currently ill. Participants were also screened and excluded for the presence of any possible COVID-19 symptoms (based on CDC guidelines at the time of data collection in 2022, such as fever, cough, sore throat, shortness of breath, loss of taste or smell in the past five days, vomiting or diarrhea, repeated shaking with chills, or any current upper respiratory symptoms, such as a runny or stuffy nose). Participants were excluded if they had contracted (i.e., tested positive or come in close physical contact with someone who tested positive) with

³ Fifty-nine participants consented to participate, but we only have complete data from fifty-five participants, and henceforth report on the sample of 55. Of the four participants missing post-vaccine data, two withdrew from the study after the pre-vaccine session, one failed to attend their post-vaccine session, and one was unable to attend their post-vaccine session due to inclement weather.

⁴ Five participants endorsed more than one race/ethnicity and are represented in the frequency and percentage for *each* racial category they selected.

COVID-19 in the past two weeks.

2.2. Procedure

Participants provided informed consent over Zoom teleconferencing software. They were scheduled to complete two study sessions scheduled approximately 24-h apart (pre-vaccine and post-vaccine), all occurring between 8AM and 1PM (based on procedures from other studies, Kuhlman et al., 2018; Radin et al., 2021). Participants received instructions prior to their first session, specifically to get a good night's sleep, to eat a satisfying meal prior to the session (i.e., no fasting), to be well-hydrated, and to bundle up if it was cold. Participants were also instructed not to exercise the morning of the session, not to use over-the-counter medication the night before or morning of the session, and not to intake caffeine in the two hours prior to their session. The day prior to the pre-vaccine session and during the day following the post-vaccine session, participants completed multiple brief momentary reports (details below). For both sessions in the lab, participants completed computer tasks (not relevant to the present paper), answered surveys, and had their ring-finger pricked to provide 20 μ L of blood, collected with Neoteryx's Mitra Clamshell (<https://www.neoteryx.com/mitra-clamshell-blood-collection-device?hsLang=en>). At the end of the pre-vaccine session, participants received the annual influenza vaccine. The influenza vaccine administered was a 0.5 mL single-dose of GSK's Flulaval Quadrivalent and included the following virus strains: A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), B/Brisbane/60/2008 (Victoria lineage). Participants were compensated \$107.

2.3. Measures

2.3.1. Inflammation

Blood samples were dried overnight and stored in a -80°C freezer until study completion, then assayed in triplicate for levels of IL-6 using high-sensitivity ELLA immunoassay platform (R&D Systems). All samples were detectable, ranging from 0.56–2.37 pg/mL pre-vaccine and 0.59–2.4 pg/mL post-vaccine. Across all three assay plates, the intra-assay coefficient of variation (CV) was 5.8% and the inter-assay coefficient of variation was $<12\%$.

2.3.2. Momentary social connection

Participants completed five brief (~ 3 -minute) momentary reports over the day preceding their pre-vaccine session, and three reports over the day following their post-vaccine session (Fig. 1). Participants also completed four momentary reports over the course of the day following their pre-vaccine session (i.e., over the 9 subsequent hours following the session); however, those reports were excluded from analysis. We chose to exclude these reports because they were assessed after the influenza vaccine was administered, but before participants had likely reached their peak inflammatory response 24-h later (Radin et al., 2021), and thus, it is unclear if these reports likely corresponded with pre-vaccine IL-6 levels, post-vaccine IL-6 levels, or IL-6 reactivity.

Prior to receiving the first momentary report, participants selected a non-familial close other (e.g., romantic partner, close friend, roommate) whom they saw every day and whom they “could go to for help or for comfort” (n close friends/roommates = 41, n romantic partners = 14).⁵ Participants answered the same set of questions about this close other for each report, focusing on the time since the last report. Participants

provided the nickname, initials, or moniker for this close other, which was piped into each question and will be represented in the measures as '[close other]'. Questions were designed to capture a constellation of social connection-related thoughts, feelings, and behaviors in that moment: (1) *Desire to be near*: “how much did you want to be near or around [close other]?”, measured from *not at all* (1) to *a great deal* (5); (2) *Felt comfort/reassurance*: “how much did [close other] make you feel better (either by providing comfort or reassurance, either in person or remotely)?”, measured from *not at all* (1) to *a great deal* (5); (3) *Affectionate touch*: “how much did you engage in affectionate touch with [close other]? e.g., hugged, sat close together, held hands, high fived”, measured from *not at all* (1) to *a great deal* (5); (4) *Overall spontaneous thoughts*: “how many times did you have spontaneous thoughts—the kind that pop into your head or surface without much effort—about interacting with or being near [close other]?”, measured from *never* (1) to *frequently* (5); (5) *Proportion positive spontaneous thoughts*: “what proportion of the spontaneous thoughts were: *pleasant or positive*”, answered on a slider from 0 to 100; (6) *Proportion negative spontaneous thoughts*: “what proportion of the spontaneous thoughts were: *unpleasant or negative*”, answered on a slider from 0 to 100; (7) *Relationship quality*: “My relationship with close other is:” measured from *terrible* (1) to *terrific* (9).

2.4. Statistical analyses

Three IL-6 values were more than 3 SDs above the mean and were winsorized and retained in the data. Then, IL-6 values were log-transformed for analyses. All analyses controlled for biological sex, BMI,⁶ relationship type of the close other (close friend/roommate or romantic partner), and report number (when relevant, see below). All analyses were conducted in R.

2.4.1. IL-6 reactivity

IL-6 reactivity was computed by subtracting log-transformed pre-vaccine IL-6 from log-transformed post-vaccine IL-6. IL-6 reactivity was used to predict each separate post-vaccine momentary social connection experience variable, controlling for aggregated pre-vaccine reports of the same variable. In order to harness the full power of our repeated measures design, we fit two-level multilevel models using the lmer function in the lme4 package in R (Bates et al., 2014), regressing the nested Level 1 social connection outcome on Level 2 predictors of IL-6 reactivity, biological sex, BMI, and relationship type. Additionally, pre-vaccine social connection reports were aggregated (for each measure separately) and entered as a Level 2 predictor in the reactivity models. These models are consistent with analytic approaches from other work using IL-6 reactivity to the influenza vaccine to predict change in post-vaccine psychosocial outcomes (controlling for pre-vaccine levels of those outcomes; Feldman et al., 2023; Kuhlman et al., 2018). Finally, because pre-vaccine IL-6 levels and IL-6 reactivity were significantly negatively correlated ($r = -.66$, $p < .001$), we also controlled for pre-vaccine IL-6 levels in reactivity models, following recommended best practices when using change scores in analyses (Dalecki and Willits, 1991; Llabre et al., 1991; O'Connell et al., 2017). Models unadjusted for pre-vaccine IL-6 are in Supplemental Materials (SM; Supplementary Tables 23–29).

2.4.2. IL-6 levels

To assess how IL-6 levels were concurrently associated with indicators of social connection, we fit two-level multilevel models to account for the nesting of multiple reports within participant. Each social

⁵ The selected close other was generally a high-quality support figure for participants, indicated by participant's average rating of 6.4 (out of a 7-point scale, range = 4.5–7) on two items measured at baseline: 1) Can you rely on this person for help if you have a serious problem? 2) Can you really count on this person to help you feel better when you are feeling generally down-in-the-dumps?

⁶ The accuracy of BMI measurement can be influenced age, sex, race/ethnicity, muscle mass and other factors, and readers should interpret this measure with caution. For more information on considerations of BMI metrics, see <https://www.cdc.gov/obesity/downloads/bmiforpractitioners.pdf>

Study Timeline and Momentary Report Schedule

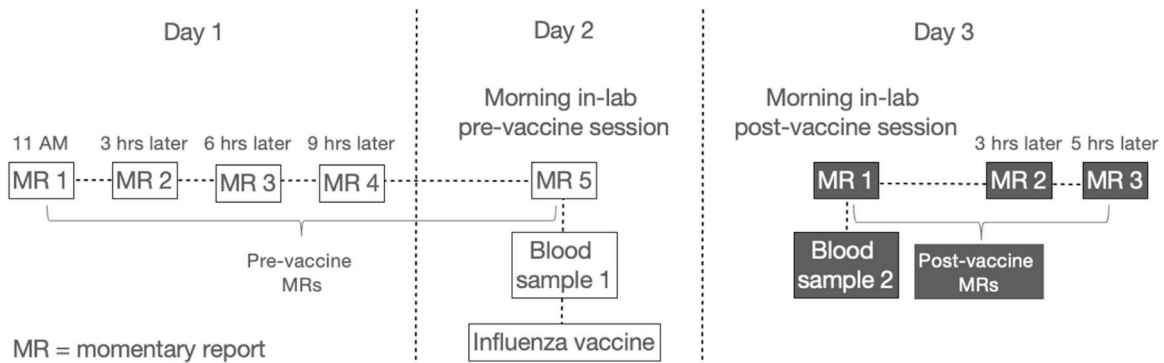


Fig. 1. Study timeline and pre- and post-vaccine momentary report administration schedule.

connection variable was separately regressed on IL-6. Thus, within one model, pre-vaccine IL-6 predicted multilevel pre-vaccine momentary social connection reports, and post-vaccine IL-6 predicted multilevel post-vaccine momentary social connection reports. Notably, we did not measure IL-6 at every timepoint momentary social connection was measured. To circumvent this inherent limitation, we treated pre-vaccine IL-6 as stable (i.e., the same value) at each of the pre-vaccine momentary social connection timepoints, and post-vaccine IL-6 as stable (i.e., the same value) at each of the post-vaccine momentary social connection timepoints. However, it is worth noting that IL-6 levels are expected to begin returning to baseline after approximately 24-h post-vaccine (Radin et al., 2021). We consider assessments of IL-6 and reported connection experiences to be measured *concurrently* within pre-vaccine and within post-vaccine measurements; we do not attempt to interpret results of these analyses in terms of directional change.

2.4.3. Ancillary models

We conducted additional models to provide a more comprehensive picture of results. We explored moderation of IL-6 by relationship type (friend versus romantic partner) and separately, moderation of IL-6 by

biological sex (female versus male). Next, we ran models including hormonal contraceptive use as an additional covariate. Finally, we ran models including the time-of-day participants had their blood collected (i.e., inflammation measured) as an additional covariate. All ancillary model results can be found in SM.

2.4.4. Power

We ran post-hoc simulated power analyses using *mixedpower* in R (Kumle et al., 2021). Linear mixed models for each of the seven social connection outcomes revealed felt comfort/reassurance and relationship quality were sufficiently powered with our sample size of 55 ($>.80$), desire to be near was moderately powered ($=.51$), and affectionate touch and the three spontaneous thoughts items (i.e., overall frequency, proportion positive, proportion negative) were underpowered to detect effects of IL-6. See [Supplementary Tables 1–7](#) for estimated power at each simulated sample size for each social connection outcome.

3. Results

IL-6 significantly increased from pre- to post-vaccine, $F(1,50)=$

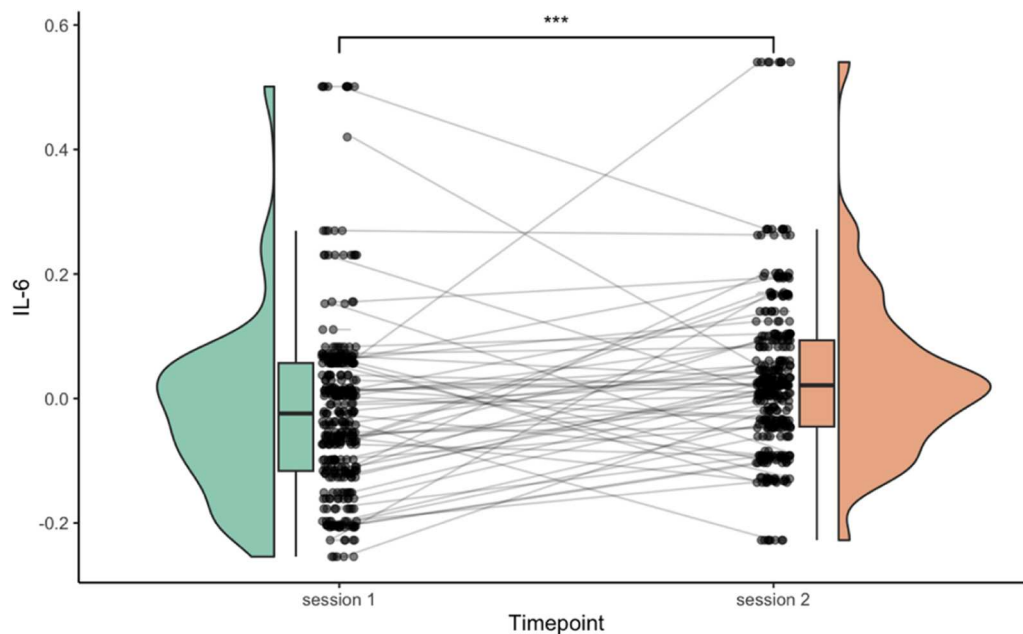


Fig. 2. Each participant's log-transformed IL-6 values for Session 1 (left-side) and Session 2 (right-side). Box and whisker plot depicts the mean and distribution for both IL-6 measurements.

11307, $p < .001$, $\eta^2 = .96$, controlling for biological sex and BMI. Thirty-nine out of 55 participants (71%) increased in IL-6 from pre- to post-vaccine (see Fig. 2).

3.1. IL-6 reactivity

Consistent with other work using the influenza vaccine as a mild inflammatory challenge (Boyle et al., 2019; Jolink et al., 2022; Kuhlman et al., 2018), we first examined if IL-6 reactivity to the influenza vaccine was associated with changes in momentary social connection from pre-vaccine to post-vaccine. Overall, IL-6 reactivity to the influenza vaccine was not associated with changes in momentary social connection post-vaccine for most of the social connection variables (affectionate touch: $b = .49$, $p = .52$; desire to be near the close other, $b = 1.51$, $p = .09$; felt comfort and reassurance, $b = 1.79$, $p = .09$; overall spontaneous thoughts: $b = .62$, $p = .46$; proportion of positive spontaneous thoughts: $b = 1.92$, $p = .91$; proportion of negative spontaneous thoughts: $b = 18.85$, $p = .55$). However, greater IL-6 reactivity was associated with significantly higher relationship quality post-vaccine (controlling for pre-vaccine relationship quality), $b = 1.35$, $p = .03$.

3.2. IL-6 levels

Next, we conducted concurrent analyses to examine how IL-6 levels were related to temporally proximal momentary experiences of social connection across our two assessment timepoints. IL-6 levels were positively associated with being made to feel better by the close other,

$b = 1.92$, $p = .004$. Specifically, those with higher levels of IL-6 (regardless of pre- or post-vaccine) reported feeling more momentary comfort and reassurance from their close other. Levels of IL-6 were also positively associated with desire to be near the close other, $b = 1.31$, $p = .02$, such that those with higher IL-6 levels reported a greater momentary desire to be near or around their close other. IL-6 levels were not associated with affectionate touch, $b = .62$, $p = .19$, or with either overall frequency of spontaneous thoughts, $b = .14$, $p = .81$, or the proportion of spontaneous thoughts that were positive, $b = 19.41$, $p = .14$, or negative, $b = -8.44$, $p = .41$. Finally, IL-6 was positively associated with relationship quality, $b = 1.58$, $p < .001$, such that those with higher IL-6 levels reported feeling more momentary satisfaction in their relationship. See Fig. 3 for plots of significant associations between IL-6 and momentary social connection with the close other.

3.3. Ancillary models

We conducted additional models to provide a more comprehensive picture of the results. We first explored interactions between IL-6 and relationship type in predicting each social connection experience (see Supplemental Materials for full results). No significant interactions emerged except for affectionate touch: IL-6 x relationship type, $b = 2.94$, $p = .002$. Probing simple slopes revealed the slope of IL-6 on touch was significantly different from zero and positive only for those reporting about romantic partners ($b = 2.77$, $p < .001$), not friends/roommates ($b = -.18$, $p = .74$).

Next, we explored potential moderation by biological sex and did not

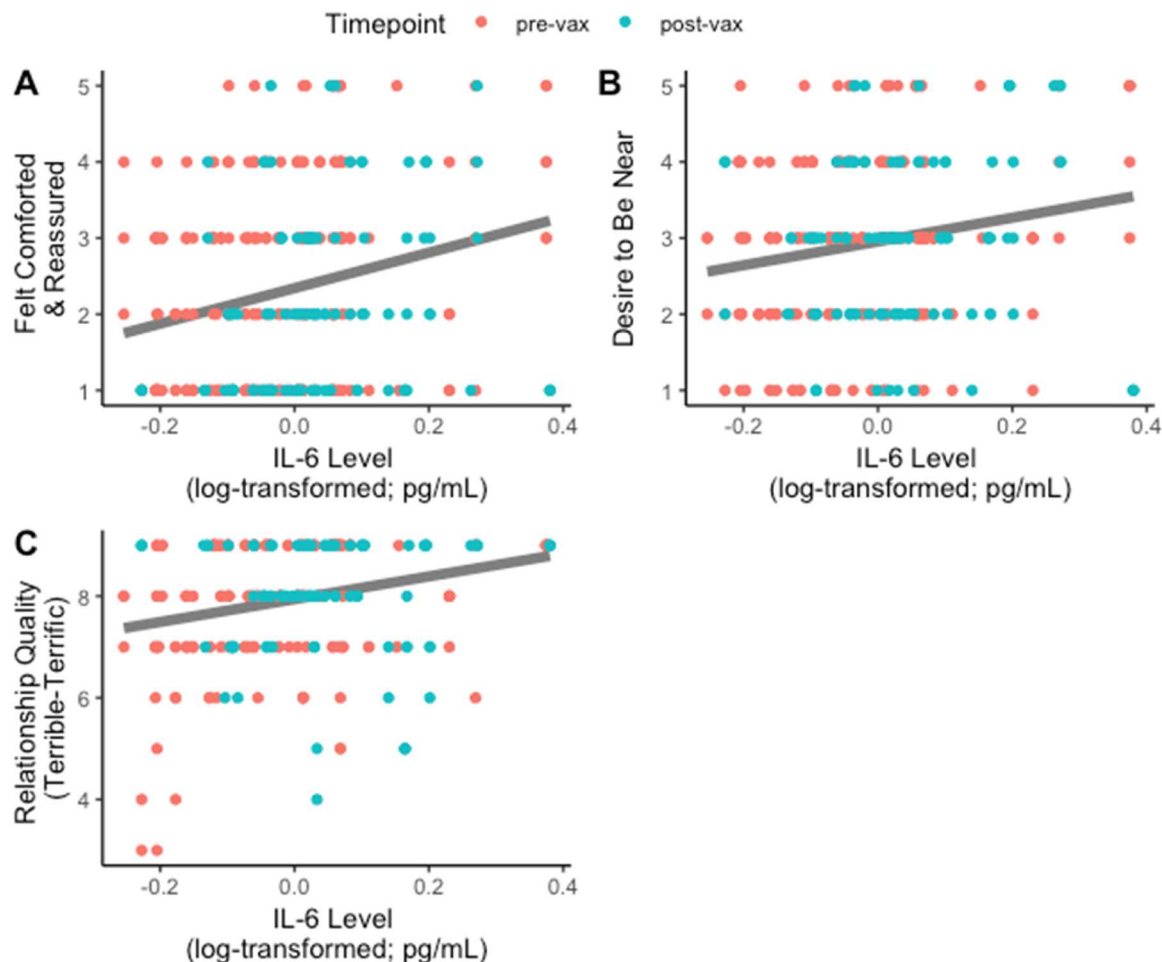


Fig. 3. Significant associations between IL-6 and momentary social connection experiences. IL-6 levels (both pre/post vaccine) positively associated with reports of (a) feeling more comforted and reassured, (b) greater desire to be near, and (c) higher relationship quality with a participant's close other in the moment.

find evidence that results were moderated (i.e., we found no significant interactions between IL-6 levels x sex or IL-6 reactivity x sex on any of the momentary social connection measures). See [Supplementary Tables 30–43](#). Next, we ran models that accounted for hormonal contraceptive use as an additional covariate; all significant effects remained significant with the addition of this covariate. See [Supplementary Tables 44–57](#) for details. Finally, we accounted for potential differences in inflammation based on time of day by including the time participants had their blood collected (i.e., when inflammation was measured) as an additional covariate; for reactivity models, we included the difference in the time of day between the two blood collections/inflammation measurements as the covariate. All significant effects remained significant when accounting for time-of-day; see [Supplementary Tables 58–71](#).

4. Discussion

The present study investigated associations between IL-6 and momentary social connection-related thoughts, feelings, and behaviors toward a close other in daily life. We found that higher levels of IL-6 were associated with greater experiences of momentary social connection (feeling comforted and reassured, desire to be near, relationship quality) toward a specific close other. These findings add to the growing literature suggesting higher inflammation may promote approaching a social target when said target is a *close other* ([Muscatell and Inagaki, 2021](#)). This study is also one of the first to use momentary reports to measure real-time social connection experiences with a close other in the context of inflammation, giving us a more comprehensive picture of how IL-6 associates with momentary experiences of connecting with those we are closest to.

It is intriguing that higher levels of IL-6 were associated with greater felt comfort and reassurance from a close other, as this fits with theory that one reason inflammation may promote approach toward support figures is that they can provide comfort during recuperation. Further, the association between higher IL-6 and a greater desire to be near the close other is consistent with prior work which found that individuals reported feeling greater desire to be near a support figure (e.g., “like being around [their support figure] right now”) following lipopolysaccharide exposure ([Inagaki et al., 2015](#)), which experimentally induces an inflammatory response. We also found both higher levels of IL-6 and greater IL-6 reactivity to the influenza vaccine were associated with higher relationship quality (e.g., feeling like one’s relationship is currently more “terrific” than “terrible”). Although speculative, experiencing heightened inflammation may signal the need to identify and seek support from an established close other. Thus, it may be evolutionarily adaptive for us to have positive impressions of those close others at a time when we may be more physiologically vulnerable. This idea fits with other pre-clinical work showing animals demonstrating social contact with close conspecifics during heightened inflammation or sickness ([Aubert, 1999](#); [Hennessy et al., 2014](#); [Willette et al., 2007](#); [Yee and Prendergast, 2010](#)). Furthermore, these results speak to existing close relationships research. We postulate experiencing heightened inflammation is likely not signaling the need to identify potential *new* close others (e.g., go on a first date), but rather motivating us to draw toward those with whom we already share a strong bond, although future research is needed to explicitly examine this ([Lindsay, 2022](#); [Muscatell and Inagaki, 2021](#)).

It is important to note that not all indicators of social connection emerged as significantly related to IL-6 levels. For instance, we did not find IL-6 levels were associated with affectionate touch or any spontaneous thoughts about one’s close other. Notably, those effects were the most underpowered, so it could be the case that those associations would emerge as significant in a larger sample. It could also be the case that the three items about spontaneous thoughts may have been a bit cognitively abstract and difficult for participants to answer, as estimating the frequency of spontaneous thoughts is not something we are regularly asked to do. Regardless, the discriminant findings across the individual social

connection measures further emphasize the importance of precise and proximal measurement of social connection experiences. This is especially true in light of the fact that prior studies with general, holistic measures of social connection have not found associations with IL-6 reactivity to the influenza vaccine ([Jolink et al., 2022](#); [Kuhlman et al., 2018](#)), suggesting that levels of/changes in markers of inflammation may be related to more *specific* indicators of connection with a close other, but not broader perceptions of social connection writ large. Altogether, the current work provides initial evidence that IL-6 levels and certain indicators of connection with close others are positively linked in daily life.

Despite positive associations between IL-6 levels and various indicators of momentary social connection, IL-6 reactivity was not associated with most measures of social connection except relationship quality. This is perhaps because the sample demonstrated a smaller magnitude of change in the inflammatory response to the influenza vaccine compared to prior work ([Kuhlman et al., 2018](#); [Radin et al., 2021](#)), or due to a lack of statistical power. Further, because individuals were reporting on high-quality relationships (e.g., high levels of connection at baseline), some of our social connection measures may have shown ceiling effects. Regardless, more work is needed on the association between mild fluctuations in IL-6 (i.e., reactivity) and momentary social connection with a close other.

This work advances knowledge that the immune system is relevant for proximal psychosocial processes, often measured using ecological momentary assessment methods. Recent work by [Graham-Engeland \(2018, 2022\)](#) has demonstrated associations between momentary measures of negative affect or mood and inflammation that differ from associations between recalled affect/mood measures and inflammation (i.e., no association or a weaker association when using recall than when using momentary assessments). While the link between affect in daily life and inflammation has been established ([Jones et al., 2020](#); [Steptoe et al., 2008](#); for review, [Jones and Graham-Engeland, 2021](#)), very little research has examined other social processes on a daily and within-day level (for exceptions, see [Bajaj et al., 2016](#); [Kuhlman et al., 2018](#)). The present findings document some of the first evidence to our knowledge using momentary, proximal measures of relationship processes in a study on the immune system, in order understand how momentary social connection experiences are associated with levels and changes in IL-6.

While it was beyond the scope this study to test for sex differences in the association between interleukin-6 and momentary social connection, it is possible we would have seen differences between males and females in a larger sample. Prior work has found sex differences in the psychological and neural consequences of an inflammatory challenge ([Eisenberger et al., 2009](#); [Lasselin et al., 2018](#)), including females who received an endotoxin (v. placebo) demonstrating greater increases in self-reported depressive mood ([Moieni et al., 2015](#)), self-reported social disconnection ([Eisenberger et al., 2009](#); [Moieni et al., 2015](#)), and decreased ventral striatum activity in anticipation of a monetary reward ([Moieni et al., 2019b](#)), compared to males. In contrast, males may be more sensitive to inflammation-induced changes in social status, as evidenced by males’ decreased perceptions of social status after receiving an endotoxin, an effect not found in females ([Moieni et al., 2019a](#)). Future research should examine potential sex differences in proximal social behavior as related to levels and changes of IL-6.

4.1. Limitations

One limitation of this work is that it is correlational, and we interpret IL-6 and social connection as being measured concurrently in the IL-6 levels models (before and after the vaccine, respectively). Thus, we do not attempt to interpret our results as change, nor do we claim to test causality, and we encourage future work to unpack the temporal ordering of these effects. On that point, a methodological limitation of the study was the timing of the momentary reports. Specifically, the pre-

vaccine momentary reports were collected *prior* to the pre-vaccine IL-6 measurement while the majority of the post-vaccine momentary reports were collected after the post-vaccine IL-6 measurement. This timing should be improved in future work. Despite this limitation, we see these findings as important preliminary evidence of the link between IL-6 and momentary experiences with a close other, but improving the timing of each assessment would provide greater clarity on how tightly these microprocesses are associated in daily life. For example, a future study measuring IL-6 concurrently across multiple momentary timepoints across multiple days would be a major advancement for the field.

Additionally, our decision to use IL-6 as the marker of inflammation in this study was based on prior research, though we acknowledge that focusing on levels of a single cytokine limits the conclusions that can be drawn about “inflammation” more broadly. However, given that prior work using the influenza vaccine has also exclusively focused on IL-6 (Boyle et al., 2019; Feldman et al., 2023; Jolink et al., 2022; Kuhlman et al., 2018; Radin et al., 2021), and given that it is the only cytokine for which we currently know the time course of reactivity to the flu vaccine (Radin et al., 2021), it made good methodological sense to focus on IL-6 in the present study. Further, examining IL-6 allows us to be in dialogue with other work in this area more broadly, which also regularly examines levels of IL-6 as related to psychological processes (e.g., SES and inflammation, Muscatell et al., 2020; psychological stress and inflammatory reactivity, Marsland et al., 2017; social support and inflammation, Uchino et al., 2018).

An additional limitation is our sample size. Although our post-hoc simulated power analyses revealed that two of our significant effects (i.e., felt comfort and reassurance and relationship quality) were well powered to detect effects, one effect (i.e., desire to be near) was slightly underpowered. However, all results could be considered preliminary evidence and will need to be replicated in the future (e.g., using the influenza vaccine as an *experimental* between-subjects inflammatory challenge). Next, we did not collect adequate information about menstrual cycling among female participants to be able estimate the specific menstrual cycle phase participants were in at the time of the study for use as a covariate. This is a limitation that should be addressed in future work. However, we did explore contraceptive use as an additional control variable; controlling for birth control did not negate any significant effects of IL-6 on social connection. Future work should more thoroughly integrate the measurement of female's cycle phase and/or contraceptive use at the outset of the study.

Next, while we labeled the constellation of items used in this study as *momentary experiences of social connection*, we did not explicitly measure social connection (e.g., how connected do you feel to this person?), and we also recognize certain items of the seven utilized may correlate better to a broad factor of social connection than others. Lastly, the sample consisted of healthy college students below the age of 25, and future work should attempt to replicate these findings in more representative samples.

5. Conclusion

The current study used ecologically-valid momentary reporting of social connection experiences to test the association between IL-6 and thoughts, feelings, and behavior toward a proximal, close other. By demonstrating an association between higher IL-6 levels and a constellation of social connection indicators, we advance theoretical and empirical understanding of how inflammation may promote social approach toward our closest others.

Funding and acknowledgements

The authors would like to thank the participants who generously gave their time and the research assistants who helped collect the data. This work was supported by the Ann Rankin Cowan Excellence Award for High Impact Research awarded to Dr. Muscatell by UNC-CH

Department of Psychology and Neuroscience. The composition of this manuscript was supported by the National Science Foundation CAREER Grant (BCS2047344 awarded to Dr. Muscatell).

IRB

The study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

CRediT authorship contribution statement

Gabriella M. Alvarez: Writing – review & editing, Visualization, Investigation. **Taylor N. West:** Writing – review & editing, Investigation. **Tatum A. Jolink:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization, Investigation. **Keely A. Muscatell:** Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization, Investigation. **Sara B. Algoe:** Writing – review & editing. **Mallory J. Feldman:** Writing – review & editing, Visualization, Investigation. **Megan N. Cardenas:** Writing – review & editing, Investigation.

Declaration of Competing Interest

none

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psychneuen.2024.107020](https://doi.org/10.1016/j.psychneuen.2024.107020).

References

- Aubert, A., 1999. Sickness and behaviour in animals: a motivational perspective. *Neuroscience & Biobehavioral Reviews* 23 (7), 1029–1036.
- Bajaj, A., John-Henderson, N.A., Cundiff, J.M., Marsland, A.L., Manuck, S.B., Kamarck, T. W., 2016. Daily social interactions, close relationships, and systemic inflammation in two samples: Healthy middle-aged and older adults. *Brain Behav. Immun.* 58, 152–164.
- Yee, J.R., Prendergast, B.J., 2010. Sex-specific social regulation of inflammatory responses and sickness behaviors. *Brain, Behavior, and Immunity* 24 (6), 942–951.
- Bates, D., Mächler, M., Bolker, B., & Walker, S. (2014). Fitting linear mixed-effects models using lme4. *arXiv preprint arXiv:1406.5823*.
- Boyle, C.C., Kuhlman, K.R., Dooley, L.N., Haydon, M.D., Robles, T.F., Ang, Y.S., Pizzagalli, D.A., Bower, J.E., 2019. Inflammation and dimensions of reward processing following exposure to the influenza vaccine. *Psychoneuroendocrinology* 102, 16–23.
- Cameron, L.D., Overall, N.C., 2018. Suppression and expression as distinct emotion-regulation processes in daily interactions: Longitudinal and meta-analyses. *Emotion* 18 (4), 465.
- Carty, C.L., Heagerty, P., Nakayama, K., McClung, E.C., Lewis, J., Lum, D., Jarvik, G.P., 2006. Inflammatory response after influenza vaccination in men with and without carotid artery disease. *Arterioscler. Thromb. Vasc. Biol.* 26 (12), 2738–2744.
- Chang, Y.P., Way, B.M., Sheeran, P., Kurtz, L.E., Baucom, D.H., Algoe, S.B., 2022. Implementation intentions to express gratitude increase daily time co-present with an intimate partner, and moderate effects of variation in CD38. *Sci. Rep.* 12 (1), 1–11.
- Christian, L.M., Iams, J.D., Porter, K., Glaser, R., 2011. Inflammatory responses to trivalent influenza virus vaccine among pregnant women. *Vaccine* 29 (48), 8982–8987.
- Christian, L.M., Porter, K., Karlsson, E., Schultz-Cherry, S., Iams, J.D., 2013. Serum proinflammatory cytokine responses to influenza virus vaccine among women during pregnancy versus non-pregnancy. *Am. J. Reprod. Immunol.* 70 (1), 45–53.
- Dalecki, M., Willis, F.K., 1991. Examining change using regression analysis: Three approaches compared. *Sociol. Spectr.* 11 (2), 127–145.
- DellaGioia, N., Hannestad, J., 2010. A critical review of human endotoxin administration as an experimental paradigm of depression. *Neurosci. Biobehav. Rev.* 34 (1), 130–143.
- Ditzen, B., Hoppmann, C., Klumb, P., 2008. Positive couple interactions and daily cortisol: On the stress-protecting role of intimacy. *Psychosomatic medicine* 70 (8), 883–889.
- Edwards, K.M., Burns, V.E., Reynolds, T., Carroll, D., Drayson, M., Ring, C., 2006. Acute stress exposure prior to influenza vaccination enhances antibody response in women. *Brain Behav. Immun.* 20 (2), 159–168.
- Eisenberger, N.I., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2009. An fMRI study of cytokine-induced depressed mood and social pain: the role of sex differences. *Neuroimage* 47 (3), 881–890.

- Eisenberger, N.I., Moieni, M., Inagaki, T.K., Muscatell, K.A., Irwin, M.R., 2017. In sickness and in health: the co-regulation of inflammation and social behavior. *Neuropsychopharmacology* 42 (1), 242–253.
- Feldman, M.J., Jolink, T.A., Alvarez, G.M., Fendinger, N.J., Gaudier-Diaz, M.M., Lindquist, K.A., Muscatell, K.A., 2023. The roles of inflammation, affect, and interoception in predicting social perception. *Brain, Behavior, and Immunity* 112, 246–253.
- Graham-Engeland, J., DeMeo, N.N., Jones, D.R., Mathur, A., Smyth, J.M., Sliwinski, M.J., Engeland, C.G., 2022. Individuals with both higher recent negative affect and physical pain have higher levels of C-reactive protein. *Brain Behav. Immun. -Health* 21, 100431.
- Graham-Engeland, J.E., Sin, N.L., Smyth, J.M., Jones, D.R., Knight, E.L., Sliwinski, M.J., Engeland, C.G., 2015. Negative and positive affect as predictors of inflammation: Timing matters. *Brain Behav. Immun.* 74, 222–230.
- Hennessy, M.B., Deak, T., Schiml, P.A., 2014. Sociality and sickness: have cytokines evolved to serve social functions beyond times of pathogen exposure? *Brain Behav. Immun.* 37, 15–20.
- Inagaki, T.K., Muscatell, K.A., Irwin, M.R., Cole, S.W., Eisenberger, N.I., 2012. Inflammation selectively enhances amygdala activity to socially threatening images. *Neuroimage* 59 (4), 3222–3226.
- Inagaki, T.K., Muscatell, K.A., Irwin, M.R., Moieni, M., Dutcher, J.M., Jevtic, I., Eisenberger, N.I., 2015. The role of the ventral striatum in inflammatory-induced approach toward support figures. *Brain Behav. Immun.* 44, 247–252.
- Jolink, T.A., Fendinger, N.J., Alvarez, G.M., Feldman, M.J., Gaudier-Diaz, M.M., Muscatell, K.A., 2022. Inflammatory reactivity to the influenza vaccine is associated with changes in automatic social behavior. *Brain Behav. Immun.* 99, 339–349.
- Jolink, T.A., Way, B.M., Younge, A., Oveis, C., Algoe, S.B., 2023. Everyday co-presence with a romantic partner is associated with lower C-reactive protein. *Brain Behav. Immun.* 107, 132–139.
- Jones, D.R., Graham-Engeland, J.E., 2021. Positive affect and peripheral inflammatory markers among adults: a narrative review. *Psychoneuroendocrinology* 123, 104892.
- Jones, D.R., Smyth, J.M., Engeland, C.G., Sliwinski, M.J., Russell, M.A., Sin, N.L., Graham-Engeland, J.E., 2020. Affect variability and inflammatory markers in midlife adults. *Health Psychol.* 39 (8), 655.
- Kamarck, T.W., Schwartz, J.E., Shiffman, S., Muldoon, M.F., Sutton-Tyrrell, K., Janicki, D.L., 2005. Psychosocial stress and cardiovascular risk: what is the role of daily experience? *J. Personal.* 73 (6), 1749–1774.
- Kane, H.S., Slatcher, R.B., Reynolds, B.M., Repetti, R.L., Robles, T.F., 2014. Daily self-disclosure and sleep in couples. *Health Psychology* 33 (8), 813.
- Kornienko, O., Riis, J., Davila, M., White, N.S., Garner, P.W., 2022. Preliminary insights into associations between C-reactive protein and social network dynamics. *Psychoneuroendocrinology* 139, 105690.
- Kuhlman, K.R., Robles, T.F., Dooley, L.N., Boyle, C.C., Haydon, M.D., Bower, J.E., 2018. Within-subject associations between inflammation and features of depression: Using the flu vaccine as a mild inflammatory stimulus. *Brain Behav. Immun.* 69, 540–547.
- Kumle, L., Vö, M.L.H., Draschkow, D., 2021. Estimating power in (generalized) linear mixed models: An open introduction and tutorial in R. *Behav. Res. Methods* 53 (6), 2528–2543.
- Lacourt, T.E., Houtveen, J.H., Van Zanten, J.V., Bosch, J.A., Drayson, M.T., Van Doornen, L.J.P., 2015. Negative affectivity predicts decreased pain tolerance during low-grade inflammation in healthy women. *Brain Behav. Immun.* 44, 32–36.
- Lasselin, J., Lekander, M., Axelsson, J., Karshikoff, B., 2018. Sex differences in how inflammation affects behavior: what we can learn from experimental inflammatory models in humans. *Front. Neuroendocrinol.* 50, 91–106.
- Lindsay, E.K., 2022. Small "doses" of inflammation initiate social sickness behavior. *Brain Behav. Immun.* 102, 40–41.
- Lindsay, E.K., Inagaki, T.K., Walsh, C.P., Messay, B., Ewing, L.J., Marsland, A.L., 2022. Stress-related inflammation and social withdrawal in mothers of a child with cancer: a 1-year follow-up study. *Psychosom. Med.* 84 (2), 141–150.
- Llabre, M.M., Spitzer, S.B., Saab, P.G., Ironson, G.H., Schneiderman, N., 1991. The reliability and specificity of delta versus residualized change as measures of cardiovascular reactivity to behavioral challenges. *Psychophysiology* 28 (6), 701–711.
- Madison, A.A., Way, B., Ratner, K.G., Renna, M., Andridge, R., Peng, J., Kiecolt-Glaser, J. K., 2023. Typhoid vaccine does not impact feelings of social connection or social behavior in a randomized crossover trial among middle-aged female breast cancer survivors. *Brain Behav. Immun.* 107, 124–131.
- Marsland, A.L., Walsh, C., Lockwood, K., John-Henderson, N.A., 2017. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systemic review and meta-analysis. *Brain, Behavior, and Immunity* 64, 208–219.
- Moieni, M., Irwin, M.R., Jevtic, I., Olmstead, R., Breen, E.C., Eisenberger, N.I., 2015. Sex differences in depressive and socioemotional responses to an inflammatory challenge: implications for sex differences in depression. *Neuropsychopharmacology* 40 (7), 1709–1716.
- Moieni, M., Muscatell, K.A., Jevtic, I., Breen, E.C., Irwin, M.R., Eisenberger, N.I., 2019a. Sex differences in the effect of inflammation on subjective social status: a randomized controlled trial of endotoxin in healthy young adults. *Front. Psychol.* 10, 2167.
- Moieni, M., Tan, K.M., Inagaki, T.K., Muscatell, K.A., Dutcher, J.M., Jevtic, I., Eisenberger, N.I., 2019b. Sex differences in the relationship between inflammation and reward sensitivity: a randomized controlled trial of endotoxin. *Biol. Psychiatry: Cogn. Neurosci. Neuroimaging* 4 (7), 619–626.
- Muscatell, K.A., Brosso, S.N., Humphreys, K.L., 2020. Socioeconomic status and inflammation: a meta-analysis. *Molecular psychiatry* 25 (9), 2189–2199.
- Muscatell, K.A., Inagaki, T.K., 2021. Beyond social withdrawal: New perspectives on the effects of inflammation on social behavior. *Brain Behav. Immun. -Health* 16, 100302.
- O'Connell, N.S., Dai, L., Jiang, Y., Speiser, J.L., Ward, R., Wei, W., Gebregziabher, M., 2017. Methods for analysis of pre-post data in clinical research: a comparison of five common methods. *J. Biom. Biostat.* 8 (1), 1.
- Radin, A.S., Kuhlman, K.R., Boyle, C.C., Haydon, M.D., Bower, J.E., 2021. Using the influenza vaccine as a mild, exogenous inflammatory challenge: When does inflammation peak? *Brain Behav. Immun. -Health* 13, 100239.
- Segerstrom, S.C., Hardy, J.K., Evans, D.R., Greenberg, R.N., 2012. Vulnerability, distress, and immune response to vaccination in older adults. *Brain Behav. Immun.* 26 (5), 747–753.
- Shrout, M.R., Renna, M.E., Madison, A.A., Alfano, C.M., Povoski, S.P., Lipari, A.M., Kiecolt-Glaser, J.K., 2020. Relationship satisfaction predicts lower stress and inflammation in breast cancer survivors: a longitudinal study of within-person and between-person effects. *Psychoneuroendocrinology* 118, 104708.
- Sin, N.L., Moskowitz, J.T., Whooley, M.A., 2015. Positive affect and health behaviors across five years in patients with coronary heart disease: the Heart and Soul Study. *Psychosom. Med.* 77 (9), 1058.
- Slatcher, R.B., Robles, T.F., Repetti, R.L., Fellows, M.D., 2010. Momentary work worries, marital disclosure, and salivary cortisol among parents of young children. *Psychosomatic medicine* 72 (9), 887–896.
- Stadler, G., Snyder, K.A., Horn, A.B., Shrout, P.E., Bolger, N.P., 2012. Close relationships and health in daily life: a review and empirical data on intimacy and somatic symptoms. *Psychosom. Med.* 74 (4), 398–409.
- Steptoe, A., Gibson, E.L., Hamer, M., Wardle, J., 2007. Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire. *Psychoneuroendocrinology* 32 (1), 56–64.
- Steptoe, A., O'Donnell, K., Badrick, E., Kumari, M., Marmot, M., 2008. Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women: the Whitehall II study. *Am. J. Epidemiol.* 167 (1), 96–102.
- Tsai, M.Y., Hanson, N.Q., Straka, R.J., Hoke, T.R., Ordovas, J.M., Peacock, J.M., Arnett, D.K., 2005. Effect of influenza vaccine on markers of inflammation and lipid profile. *J. Lab. Clin. Med.* 145 (6), 323–327.
- Uchino, B.N., Trettervik, R., Kent de Grey, Cronan, S., Hogan, J., Baucom, B.R., 2018. Social support, social integration, and inflammatory cytokines: A meta-analysis. *Health Psychology* 37 (5), 462.
- Willette, A.A., Lubach, G.R., Coe, C.L., 2007. Environmental context differentially affects behavioral, leukocyte, cortisol, and interleukin-6 responses to low doses of endotoxin in the rhesus monkey. *Brain, Behavior, and Immunity* 21 (6), 807–815.
- Wright, C.E., Strike, P.C., Brydon, L., Steptoe, A., 2005. Acute inflammation and negative mood: mediation by cytokine activation. *Brain Behav. Immun.* 19 (4), 345–350.