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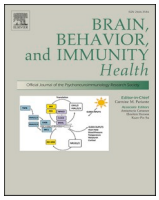

Inflammation is associated with pain and fatigue in older adults

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ABSTRACT

Introduction: Increasing evidence suggests that inflammation may play a pivotal role in the development of chronic pain and fatigue in aging individuals. This study investigated the relationship between three inflammatory markers (IL-6, CRP, and TNFα) and pain and fatigue, both cross-sectionally and longitudinally, in a sample of older adults from the Saint Louis Personality and Aging (SPAN) study.

Methods: SPAN study participants provided blood samples at two in-person sessions approximately 2 years apart for the analysis of the inflammatory biomarkers IL-6, CRP, and TNFα. Pain and fatigue were assessed using the RAND-36 Health Status Inventory. Correlations (with false discovery rate correction for multiple testing) and follow-up linear regressions including potentially confounding demographic (e.g., annual household income) and health (e.g., BMI, medication use) covariates were used to estimate cross sectional and longitudinal associations. Analytic ns ranged from 533 to 815.

Results: Cross-sectional analyses revealed that higher IL-6 and CRP were associated with greater reported pain and fatigue, even after accounting for covariates ($\beta s > .098$, $ps < .05$). TNFα was associated with greater fatigue only ($\beta = .100$, $p = .012$). Longitudinally, CRP and IL-6 predicted future pain and fatigue, although only the relationship between CRP and future fatigue survived the inclusion of covariates ($\beta = .104$, $p = .022$). Both pain and fatigue predicted higher levels of IL-6 and CRP approximately 2 years later, although only the associations with IL-6 survived the inclusion of covariates ($\beta s > .12$, $ps < .01$).

Discussion: Our study adds to a growing body of literature showing that inflammation is associated with greater pain and fatigue in older adults. Our longitudinal data showing temporal bidirectional associations is consistent with evidence from non-human animal models that heightened inflammation causally contributes to fatigue and also suggests that the experience of pain and fatigue may contribute to inflammation. It will be important for future work to identify how lifestyle factors associated with pain and fatigue (e.g., physical activity) may contribute to these associations.

1. Introduction

Aging is associated with a variety of non-specific (i.e., not tied to a specific injury or disease) health concerns that impact quality of life and functional independence. Two of the most common complaints are experiences of pain and fatigue, which frequently co-occur (Avlund et al., 2007; Cheng and Lee, 2011; Eccles and Davies, 2021). For example, up to 40% of older adults experience chronic pain that disrupts productivity, and is associated with psychiatric disorders including depression, anxiety, and substance use disorders (Larsson et al., 2017), while up to 50% of older adults complain of excess fatigue that limits physical capacity as well as cognition and emotion regulation (Yu et al., 2010). Accumulating evidence suggests that increases in inflammation associated with aging may contribute to elevated pain and fatigue among older adults (Graham et al., 2006; Renner et al., 2022).

Pain is a cardinal feature of a local inflammatory response, and inflammatory cytokines can modulate the pain threshold, leading to hyperalgesia. For example intraplantar injections of the inflammatory cytokines TNFα or IL-1β can decrease the pain threshold (Cunha et al., 1992; Safieh-Garabedian et al., 1995) and systemic inflammation induced by an endotoxin increases pain sensitivity in both humans and animals (Hutchinson et al., 2013; Karshikoff et al., 2015; Wegner et al.,

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2015). Likewise, endotoxin-induced systemic inflammation induces fatigue in rats that lasts beyond other acute sickness behaviors (Cunha et al., 1992). In humans, inflammation has been found to be independently cross-sectionally associated with fatigue in some studies (Cho et al., 2009; Valentine et al., 2009), but not others (Valentine et al., 2011), and plasma levels of the inflammatory biomarker CRP were found to be a significant predictor of fatigue 5 years later in middle-aged adults (Cho et al., 2009). Furthermore, patient populations characterized by chronic pain and/or fatigue (e.g., cervicogenic headaches, migraines, fibromyalgia, chronic fatigue syndrome) have elevated levels of inflammation (Groven et al., 2019; Koch et al., 2007; Martelletti et al., 1999; Perini et al., 2005; Pinto et al., 2023).

By better understanding the relationship between inflammation and these common and related complaints of pain and fatigue during aging, it could be possible to develop improved treatments, diagnostic tools, and preventative therapies. Here, in a relatively large community cohort study of older adults (analytic ns = 533–815), the Saint Louis Personality and Aging (SPAN) study, we examined cross sectional and bidirectional longitudinal (~2–3 years) relationships between inflammation (i.e., c-reactive protein [CRP], interleukin-6 [IL-6], and tumor necrosis factor-alpha [TNFα]) and pain and fatigue. We hypothesized that inflammation would both be associated with higher pain and fatigue and that there would be bidirectional longitudinal associations suggesting that inflammation may plausibly drive pain and fatigue, which in turn, may contribute to higher inflammation.

2. Methods

2.1. Participants and procedure

The ongoing Saint Louis Personality and Aging Network (SPAN) study is a longitudinal study of social, experiential, and biological correlates of health and personality in older adults. It began in 2007 with 1630 older adults from the Saint Louis metropolitan area (baseline data collection began in 2007 and ended in 2011; ages at baseline ranged from 54 to 65; mean ± SD 59.5 ± 2.7; 55% female; 65% White; 32% Black) using listed phone numbers that were crossed with census data to identify households with at least one member in the eligible age range (Oltmanns et al., 2014). When more than one person in a household was in the target age range, one individual was sampled at random; if the target person declined participation, we did not attempt to recruit other eligible residents in the house. Due to initial lower recruitment of Black males, additional efforts were undertaken to enhance recruitment of Black men - i.e., slightly modified letters were sent to homes in zip codes in which more than 90% of residents were Black and for which a phone number was listed under a male's name (McClendon et al., 2021). Exclusion criteria included: lack of a permanent residence, lack of fluency in English, inability to read at a 6th-grade level, or the presence of active psychotic symptoms.

Participants enrolled in the SPAN study completed an in-person interview and self-report assessment at baseline (i.e., interview and self-report questionnaires), and at four subsequent in-person follow-up (IPFU) sessions. These sessions were approximately 2–3 years apart: IPFU-1 (2010–2014; n = 1280), IPFU-2 (2014–2016; n = 1072), IPFU-3 (2016–2019; n = 1035), and IPFU-4 (ongoing; Supplemental Fig. 1). Data from the baseline assessment (see *2.5 Covariates*), as well as IPFU-2 and IPFU-3 (inflammatory biomarkers, pain and fatigue scores, covariates) were used in these analyses. The average length of time between IPFU-2 and IPFU-3 was 2.15 years (range: 20–54 months). Within two weeks of IPFU-2 and IPFU-3, a morning fasting blood draw was collected from participants agreeing to this optional study procedure. Participants received remuneration for their participation ($60 for in-person survey and interview sessions and $20 for the optional blood draw). All procedures were approved by the Washington University Institutional Review Board. Our analyses were restricted to individuals who provided IPFU-2 and/or IPFU-3 blood samples with non-missing self-report data and had data that was not excluded during quality control (see below) resulting in analytic ns from 533 to 815. See Table 1 for demographic information.

2.2. Inflammatory biomarkers

Morning fasting serum samples were collected between 7:30–10:00 a.m. via peripheral venipuncture in an independent session held within two weeks of IPFU-2 and IPFU-3 (see Bondy et al., 2021 for more detailed procedure). Samples were not collected from any participant reporting acute illness or injury. Samples were processed according to standard procedures (Tuck et al., 2009). Briefly, immediately following collection, tubes were kept upright for 40–60 min at room temperature for clots to form. Following confirmation of clot formation, samples were centrifuged at 1300 *g* for 20 min. Samples were then aliquoted into 4–8 2 mL tubes and frozen at −80 degrees C until the day of assay.

IL-6, CRP, and TNFα were assayed from serum in duplicate using commercially available enzyme-linked immunosorbent assays (IL-6: Quantikine HS Human IL-6, R&D Systems, Minneapolis, MN, USA; CRP: EIA-3954 High Sensitivity C-Reactive Protein ELISA, DRG International Inc., USA; TNFα: Quantikine HS Human TNFα, R&D Systems, Minneapolis, MN, USA). Intra- and inter-assay coeffoicients of variation were acceptable (intra-assay CVs all <8%, inter-assay CVs all <14%). Samples producing unreliable measures (i.e., intra-assay CVs>20%) of IL-6 (IPFU-2: N 38; 4.8% IPFU-3: N 7; 1.19%), CRP (IPFU-2: N 22; 2.8%; IPFU-3: N 1; .2%), or TNFα (IPFU-2: N 57; 8.7%; IPFU-3: N 4; .7%), even after being re-assayed in duplicate were excluded. Prior to analysis, inflammation markers (i.e., IL-6, CRP, and TNFα) were log transformed

Table 1
Demographic characteristics of the sample.

	IPFU-2	IPFU-3
	n = 783[a]	n = 681[a]
Demographic Variables:		
Age [mean (range)]	66 (60–73)	68 (62–75)
Sex	43.8% Male 56.2% Female	43.8% Male 56.2% Female
Race	32.2% Black 67.8% White	32.6% Black 67.4% White
BMI [mean (range)]	29.8 (15.2–70.3)	29.7 (14.3–73.0)
Annual Household Income	n (%)	
Under $20,000	70 (8.9%)	62 (9.1%)
$20,000 - $39,999	118 (15.1%)	100 (14.7%)
$40,000 - $59,999	178 (22.7%)	153 (22.5%)
$60,000 - $79,999	109 (13.9%)	101 (14.8%)
$80,000 - $99,999	81 (10.3%)	68 (10.0%)
$100,000 - $119,999	51 (6.5%)	45 (6.6%)
$120,000 - $139,9999	42 (5.4%)	32 (4.7%)
$140,000 or more	102 (13.6%)	94 (13.8%)
Medication Variables:	n (%)	
Opioids	87 (11.1%)	80 (11.7%)
Beta-blockers	157 (20.1%)	151 (22.2%)
Calcium Channel Blockers	149 (19.0%)	137 (20.1%)
ACE Inhibitors/ARBs	274 (35.0%)	224 (32.9%)
Aspirin	277 (35.4%)	211 (31.0%)
NSAIDs	139 (17.8%)	105 (15.4%)
Steroids	98 (12.5%)	81 (11.9%)
Statins	280 (35.8%)	253 (37.2%)
Outcome Variables:	mean (SD)	
Pain Score[b]	27.6 (23.5)	28.9 (23.2)
Fatigue Score[b]	38.8 (20.3)	39.4 (20.7)
IL-6 (pg/mL)[c]	2.36 (2.4)	3.02 (4.3)
TNFα (pg/mL)[c]	1.60 (.9)	1.37 (.6)
CRP (mg/L)[c]	5.17 (7.5)	3.42 (4.71)

[a] Represents number of participants with usable blood draw data.
[b] RAND-36 scale scores for pain and fatigue shown here are reverse scored, so that higher scores reflect more dysfunction. Range: 0–100.
[c] Raw data are presented here. Data were log transformed prior to analysis.

to normalize their skewed distribution, and outliers were winsorized to ± 3 standard deviations.

2.3. Pain and fatigue

Pain and fatigue were assessed via self-report on the RAND-36 Health Status Inventory (Hays and Morales, 2001) at both IPFU-2 and IPFU-3. The pain subscale of the RAND-36 consists of the average of 2 items (items 21 and 22) assessing pain and functional impairment due to pain over the past 4 weeks. The fatigue subscale consists of the average of 4 items (items 23, 27, 29, and 31) assessing energy levels over the past 4 weeks. Scoring for each RAND-36 item ranges from 0 to 100, with response-level scoring determined by the number of response options (e.g. Item 21 "How much bodily pain have you had during the past 4 weeks?" has responses ranging from 0 to 6, thus responses are scored 100 [none], 80 [very mild], 60 [mild], 40 [moderate], 20 [severe], 0 [very severe]). A higher score indicates better functioning (i.e., lower levels of pain or fatigue). To enhance clarity and ease of interpretation, we reverse-scored the RAND-36, so that higher scores in this manuscript indicate higher levels of pain and fatigue.

2.4. Change scores

Change in inflammation, pain, or fatigue was calculated by subtracting the IPFU-2 value from the IPFU-3 value, thus a positive value represents an increase in the variable (i.e., increases in pain, more fatigue, or more inflammation).

2.5. Covariates

Age. Participant age was calculated using the participant's date of birth and the date of the relevant in-person follow-up (i.e., IPFU-2 or IPFU-3, depending on the analysis). The average age at IPFU-2 was 66 (range 60–73); the average age at IPFU-3 was 68 (range 62–75).

Sex. Participants self-reported sex at the initial study baseline assessment.

Race. Two non-exclusive dummy-coded dichotomous variables were used to represent self-reported race (reported at the baseline assessment) as White/not-White and Black/not-Black.

Annual household income. Annual household income was self-reported at the baseline assessment and was coded as an ordinal variable with the following categories: (1) < $20,000, (2) $20,000–39,999, (3) $40,000–59,999, (4) $60,000–79,999, (5) $80,000–99,999, (6) $100,000–119,999, (7) $120,000–139,999, (8) > $140,000.

Body mass index. Body mass index (BMI) was calculated from participant height and weight, which were measured at the blood draw appointment.

Medication use. Medication use was assessed using self-reported lists of all current prescription drugs, over-the-counter medications, and supplements provided by participants at both IPFU-2 and IPFU-3. Medications were logged according to medication class and the following dummy-coded medication classes were included as covariates: opioids, beta-blockers, calcium channel blockers, ACE inhibitors and angiotensin receptor blockers, aspirin, NSAIDs, steroids, and statins.

2.6. Statistical analysis

Cross-sectional. We first estimated cross-sectional Pearson's correlations between inflammation (i.e., IL-6, CRP, TNFα) and health (i.e., pain and fatigue) at IPFU-2 (due to this being the largest sample size); multiple testing was adjusted for using Bonferroni correction for these 6 tests (adjusted alpha level = .05/6 = .008). We then tested whether any significant inflammation-health associations remained significant (alpha level = .05) after adjusting for potentially confounding covariates (see above; all covariates entered simultaneously) using linear regression.

Longitudinal. We estimated longitudinal correlations between our 3 inflammatory markers (i.e., IL-6, CRP, TNFα) measured at IPFU-2 and health assessed at IPFU-3 and vice versa. Any significant correlations following Bonferroni adjustment for multiple tests (n = 6), were then examined in linear regressions adjusting for potentially confounding covariates (see above).

All analyses were carried out using SPSS v. 27.

3. Results

3.1. Cross-sectional associations

All inflammatory biomarkers were significantly correlated with each other: IL-6 and CRP were moderately correlated with each other (r = .542, p < .001), and TNFα was weakly correlated with IL-6 (r = .294, p < .001) and CRP (r = .162, p < .001). With the inclusion of covariates (age, sex, race, annual household income, BMI and medication use), levels of inflammatory biomarkers were stable across timepoints (IL-6: F = 1.181, p = .278; CRP: F = 1.234, p = .267; TNFα: F = .495, p = .482) in the sub-sample of participant who completed both IPFUs. Similarly, pain and fatigue were moderately correlated (r = .539, p < .001), and, with the inclusion of covariates, both pain (F = .614, p = .314) and fatigue (F = .579, p = .447) were stable across timepoints.

Higher levels of IL-6 and CRP were associated with more pain and fatigue (rs > .22, ps < .001). TNFα was associated with higher levels of fatigue (r = .129, p = .001), but not pain (r = .050, p = .205). These findings were robust to Bonferroni correction for multiple testing and the inclusion of several demographic and medication use covariates (see Table 2, Fig. 1, Supplemental Table 1, Supplemental Table 2).

Item-level analysis for the pain subscale score, which consists of one question assessing bodily pain (item 21) and one question assessing the extent to which pain interferes with daily functioning (item 22), revealed that both items were significantly correlated with all inflammatory markers, and that effects sizes were similar for both items (Supplemental Table 3).

When the dataset was restricted to only those individuals who completed both IPFUs (i.e., had useable blood draw data for IPFU-2 and IPFU-3), cross sectional correlations between inflammatory biomarkers and pain and fatigue were consistent with the full dataset.

3.2. Longitudinal associations

Higher levels of IL-6 and CRP (rs > .16, ps < .001), but not TNFα (rs < .072, ps > .09), predicted more pain and fatigue approximately 2 years in the future (Table 3). When accounting for covariates, the association between CRP and fatigue remained significant (β = .104, p = .022). However, the association between IL-6 and fatigue was no longer significant (β = .071, p = .110), as the relationship was attenuated by annual household income, BMI, and the use of steroid medications (Supplemental Table 4). Furthermore, the association between IL-6 and future pain was reduced to a nominal trend with the inclusion of covariates (β = .076, p = .076), and the association between CRP and pain was no longer significant (β = .062 p = .158; Supplemental Table 5). These relationships were attenuated by the covariates BMI, as well the use of NSAIDs, steroids, and prescription pain medication.

Fatigue and pain each predicted higher levels of IL-6 and CRP two years later (rs > .156, ps < .001; Table 4). There was a nominal trend toward higher levels of fatigue predicting higher levels of TNFα two years later (r = .076, p = .055). After accounting for covariates, higher levels of pain and fatigue still predicted higher levels of IL-6 two years later (pain: β = .120, p = .010; fatigue: β = .130, p = .003), but the associations with CRP were no longer significant (see Table 4, Supplemental Tables 5 and 6).

Levels of IL-6, CRP, or TNFα at IPFU-2 did not predict change in pain or fatigue from IPFU-2 to IPFU-3 after adjusting for multiple correction (all ps > .47; Supplemental Table 8). Similarly, change in inflammation

Table 2
Cross-sectional Associations Between Inflammation, Pain, and Fatigue. Associations between inflammatory variables (IL-6, CRP, TNFα) and pain and fatigue, with and without the inclusion of covariates. Significant correlations ($p_{Bonferroni} < .008$ for Pearson's r values; $p < .05$ for β values) are bolded. Covariates included: age, race, gender, annual household income, BMI, beta-blockers, calcium-channel blockers, ACE inhibitors, aspirin, NSAIDs, steroids, statins, and prescription opioids.

	IL-6		CRP		TNFα	
	Without Covariates	With Covariates	Without Covariates	With Covariates	Without Covariates	With Covariates
	(r)	(β)	(r)	(β)	(r)	(β)
PAIN	**0.248**	**0.109**	**0.224**	**0.098**	.050	x
FATIGUE	**0.214**	**0.110**	**0.194**	**0.080**	**0.129**	**0.100**

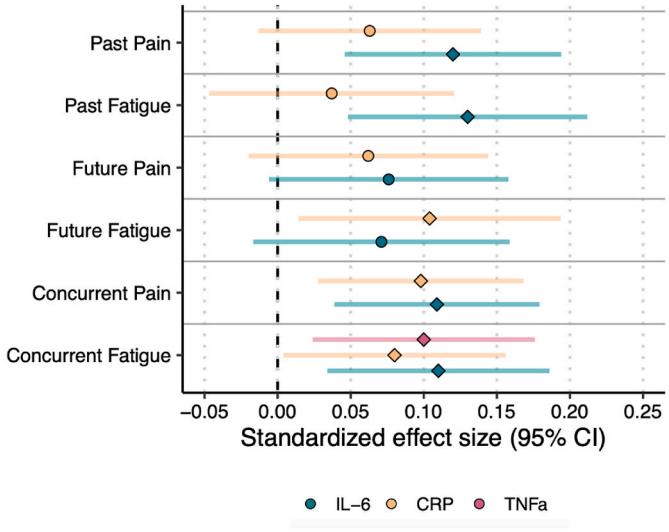

Fig. 1. Beta Estimates of Cross-sectional and Longitudinal Associations Between Inflammation, Pain, and Fatigue. Beta coefficient estimates with 95% confidence intervals for the association between health outcomes (i.e., pain and fatigue) and inflammatory markers (i.e, IL-6, CRP, and TNFα) cross-sectionally ("Concurrent") and longitudinally ("Past," wherein IPFU-2 pain/fatigue predicts IPFU-3 inflammation, and "Future," wherein IPFU-2 inflammation predict IPFU-3 pain/fatigue). Significant associations are denoted with a diamond marker (◆), non-significant associations are denoted with a circular marker (●). Covariates included: age, race, gender, annual household income, BMI, beta-blockers, calcium-channel blockers, ACE inhibitors, aspirin, NSAIDs, steroids, statins, and prescription opioids.

from IPFU-2 to IPFU-3 did not predict change in pain or fatigue (all *ps* > .03; Supplemental Table 8).

4. Discussion

Our investigation of associations between inflammation, pain, and fatigue in a community sample of older adults produced two primary results. *First*, CRP and IL-6 were each associated with increased pain and fatigue cross-sectionally; TNFα was significantly associated with fatigue, but not pain. These associations were robust to multiple testing correction and the inclusion of demographic and health-related covariates (see Table 2). Broadly, these findings replicate evidence linking inflammation to pain and fatigue in humans and the use of pro-inflammatory cytokine stimulation to model pain and fatigue in non-human animals models (Cho et al., 2009; Cunha et al., 1992; Ji et al., 2016). *Second,* our longitudinal analyses revealed evidence of bidirectional prospective relationships between inflammation and pain and fatigue. This bidirectional temporality aligns with evidence that inflammation can induce pain and fatigue in experimental studies (Hutchinson et al., 2013; Karshikoff et al., 2015; Wegner et al., 2015) and raises the possibility that pain and fatigue may also, in turn, increase inflammation. However, change in inflammation and pain and fatigue were not associated with one another.

4.1. Inflammation and pain in later life

Largely independent lines of research have shown that aging is associated with elevated inflammation and pain (Chung et al., 2009; Graham et al., 2006). However, only a few small (i.e., ns < 200) studies of pain and inflammation have been conducted in older community adult samples (Valentine et al., 2009, 2011). Here, in a relatively large sample (analytic ns = 533–815), we find that elevated CRP and IL-6 are associated with higher reported pain during the stage of later life.

Table 4
Longitudinal Associations Between Inflammation, Pain, and Fatigue. Prospective associations between pain and fatigue and inflammation measured 2 years later, with and without the inclusion of covariates. Significant correlations ($p_{Bonferroni} < .008$ for Pearson's r values; $p < .05$ for β values) are **bolded**, correlations trending toward significance ($p < .06$) are *italicized*. Covariates included: age, race, gender, annual household income, BMI, beta-blockers, calcium-channel blockers, ACE inhibitors, aspirin, NSAIDs, steroids, statins, and prescription opioids.

	PAIN (IPFU-2)		FATIGUE (IPFU-2)	
	Without Covariates	With Covariates	Without Covariates	With Covariates
	(r)	(β)	(r)	(β)
IL-6 (IPFU-3)	**0.245**	**0.120**	**0.230**	**0.130**
CRP (IPFU-3)	**0.184**	.063	**0.156**	.037
TNFa (IPFU-3)	.058	x	*0.076*	x

Table 3
Longitudinal Associations Between Inflammation, Pain, and Fatigue. Prospective associations between inflammatory variables (IL-6, CRP, and TNFα) and pain and fatigue reported 2 years later, with and without the inclusion of covariates. Significant correlations ($p_{Bonferroni} < .008$ for Pearson's r values; $p < .05$ for β values) are **bolded**, correlations trending toward significance ($p < .08$) are *italicized*. Covariates included: age, race, gender, annual household income, BMI, beta-blockers, calcium-channel blockers, ACE inhibitors, aspirin, NSAIDs, steroids, statins, and prescription opioids.

	IL-6 (IPFU-2)		CRP (IPFU-2)		TNFa (IPFU-2)	
	Without Covariates	With Covariates	Without Covariates	With Covariates	Without Covariates	With Covariates
	(r)	(β)	(r)	(β)	(r)	(β)
PAIN (IPFU-3)	**0.185**	*0.076*	**0.183**	.062	.003	x
FATIGUE (IPFU-3)	**0.168**	.071	**0.211**	**0.104**	.072	x

Furthermore, we observed that relatively elevated inflammation predicts future pain approximately 2 years later, although this association was not independent of demographic and health-related covariates. Alongside widespread evidence that inflammation induces pain (Hutchinson et al., 2013; Karshikoff et al., 2015), these data raise the intriguing possibility that typical age-related increases in inflammation (Chung et al., 2009) may contribute to elevated pain in later life (Yezierski, 2012), but that lifestyle factors, like BMI and medication use, both of which modulate inflammation, may play important, and potentially confounding roles that will require even larger samples to disentangle.

There are a host of mechanisms through which inflammation may contribute to the development and maintenance of chronic pain, with peripheral and central plasticity being a key potential mechanism. For example, cytokine-binding at somatosensory nerve terminals leads to sensitization and inflammatory pain (Gonçalves dos Santos et al., 2020). In addition to sensitizing nerve terminals, recruitment of immune cells to the spinal cord can increase the excitability of nociceptor cell bodies within the dorsal root ganglion of the spinal cord, further perpetuating pain (Chen et al., 2020; Yu et al., 2020).

Our study also found unique evidence that higher reported pain is associated with higher levels of inflammatory biomarkers approximately 2 years later. This temporality suggests that pain itself may plausibly increase inflammation, which may occur through direct or indirect mechanisms. Sensory neurons not only respond to immune signals but also directly modulate inflammation. Nociceptors, for instance, express receptors for cytokines and chemokines and produce these inflammatory mediators themselves (Ji et al., 2016). Indeed, emerging preclinical evidence shows that nociceptors directly amplify inflammation through their interaction with dendritic cells (i.e., antigen-presenting immune messenger cells). For example, Hanč and colleagues (Hanč et al., 2023) recently found that co-cultured nociceptor and dendritic cells produce elevated cytokines relative to either in isolation, with contact-dependent nociceptor stimulation of proinflammatory cytokine release from dendritic cells. In contrast, nociceptors may also constrain the immune response under certain conditions, as ablation of nociceptors has been shown to eliminate pain during bacterial infection but exacerbate other aspects of inflammation (Chiu et al., 2013). Other indirect behavioral mechanisms may also contribute to pain-related increases in inflammation. For example, pain is associated with increased sedentary behavior (Mahdavi et al., 2021) as well as weight gain (Andersen et al., 2003), which are each linked to elevated inflammation (Forsythe et al., 2008; Henson et al., 2013). Future work examining whether such pain-related changes in lifestyle partially mediate the pain-inflammation association would be informative.

4.2. Inflammation and fatigue in later life

Across species, natural immune challenges such as sickness and injury, as well as experimentally-induced inflammation generate tiredness and fatigue to facilitate rest and recovery. However, persistent fatigue commonly occurs in chronic inflammatory diseases (e.g., autoimmune diseases, obesity, cancer, and multiple sclerosis) that is disproportionate to mental or physical exertion and does not resolve with sleep (Dantzer et al., 2014). Here we find that higher CRP, IL-6, and TNFα are associated with greater fatigue among older adults, including fatigue occurring approximately 2–3 years later. These data complement findings derived from cross-sectional studies of physically ill patients (e.g., in chronic fatigue syndrome) patients linking elevated cytokine concentrations to fatigue severity (Hornig et al., 2016; Montoya et al., 2017); and provide temporal plausibility for inflammation-induced increases in fatigue. Consistent with this, interferon-alpha administration to cancer patients induces moderate-severe fatigue (Capuron et al., 2002) and TNFα antagonists significantly reduce fatigue in rheumatoid arthritis and psoriasis patients (Tyring et al., 2006; Yount et al., 2007). The mechanisms linking low-grade inflammation to fatigue remain unclear, with potential explanations encompassing changes in cellular metabolism, inhibition of orexin systems, alterations in monoamine bioavailability, and reduced sleep quality (Dantzer et al., 2014; Gaykema and Goehler, 2011; Grossberg et al., 2011; Milrad et al., 2017). Interestingly, our study also found evidence that fatigue is associated with elevated inflammation approximately 2 years later. While we are unaware of direct mechanisms through which fatigue may induce inflammation, indirect behavioral mechanisms such as fatigue-related increases in sedentary behavior (Hanna et al., 2019) and weight gain (Andersen et al., 2003) remain plausible.

4.3. Limitations and future Directions

The results of this study should be interpreted in the context of study limitations. First, while our study is relatively large for a longitudinal investigation of biomarkers and health in an older cohort, it was underpowered (i.e., <80%) to detect correlations <.10 that have been observed in studies of inflammation and complex traits (e.g., depression: (Osimo et al., 2019); this was especially the case for TNF-α, where our sample sizes were lowest. Notably, all of our effect sizes were relatively small, although this was expected given evidence of associations between inflammatory biomarkers and behavioral health outcomes (Mac Giollabhui et al., 2021). Relatedly, our community-based sample may be characterized by smaller effect associations than a patient sample. Secondly, we included medication used to treat medical conditions in our analysis that were correlated with inflammation markers in our data. It is possible that this would miss untreated chronic medical conditions that may have contributed to pain and fatigue and variability in our data. Further investigations incorporating treated and untreated medical problems are warranted to elucidate the complex interplay between health status, inflammation, and pain and fatigue. Third, while our study represents demographic factors associated with older adults in the Saint Louis region, it is predominantly composed of White and Black Americans (Table 1), leaving it unclear whether these findings may generalize to other racial groups. Fourth, we assessed limited inflammatory markers in their basal state, and it is possible that other markers (e.g., IL-1β; Ren and Torres, 2009) or evoked inflammatory responses (e.g., to a challenge such as lipopolysaccharide) may have unique associations with pain and fatigue. Fifth, while we observed correlations between inflammation and pain and fatigue, there are many interrelated behavioral variables, such as depression, that may influence this relationship. Indeed, in our sample, depression was moderately correlated with pain ($r = .415$, $p < .001$) and fatigue ($r = .580$, $p < .001$), and we have previously published on the bidirectional relationship between inflammation and depression in this sample (Bondy et al., 2021). When depression symptomatology was included as an additional covariate in supplemental analyses, many of the associations between inflammation and pain/fatigue were attenuated, although notably the relationship between CRP and pain remained significant (Supplemental Table 9). Lastly, as the SPAN study is a long-term, ongoing longitudinal assessment (currently in its 17th year), many individuals do not participate in every session or complete every follow-up. Notably, those who completed IPFU-2 but not IPFU-3 had higher CRP and IL-6 at IPFU-2 than those that completed both sessions. Similarly, those who completed IPFU-3 but did not complete IPFU-2 reported higher levels of pain than those who completed both sessions (Supplemental Table 10). It is possible that elevated health concerns associated with inflammation and increased levels of pain may prevent participants from completing assessments. This may have attenuated relationships, particularly in our longitudinal analyses.

Although our analyses revealed significant associations between inflammation and pain or fatigue when examining data longitudinally, these associations were not observed when using change scores (i.e., change in inflammation or change in pain/fatigue from IPFU-2 to IPFU-3). Multiple factors may contribute to this discrepancy. Other studies

have reported that CRP, TNFα, and IL-6 have considerable stability across years (Walsh et al., 2023), and in our own dataset we do not observe a statistically significant change in inflammation from IPFU-2 to IPFU-3, indicating limited variability in change over time. Further, change scores can potentiate measurement error, which may obfuscate associations (Tennant et al., 2022).

5. Conclusions

The present study sheds light on the intricate relationship between inflammation and two common age-related complaints – pain and fatigue. As our population ages, the importance of unraveling the biological mechanisms of age-related health concerns becomes increasingly relevant to overall public health. Our study of inflammation, pain and fatigue in older adults revealed bidirectional longitudinal associations providing temporal plausibility to potential inflammation induced increases in fatigue as well as pain-induced and fatigue-induced increases in inflammation. While inflammation-induced increases in pain and fatigue have been observed in preclinical experimental studies (e.g., Cho et al., 2009; Hutchinson et al., 2013), there has been limited study of pain and fatigue contributing to inflammation. Recent evidence has identified direct pathways through which pain may causally influence inflammation (Chiu et al., 2013; Hanč et al., 2023; Ji et al., 2016), though indirect behavioral mechanisms (e.g., pain and fatigue-related increases in sedentary behavior and weight), consistent with our findings that BMI and medication use attenuated longitudinal associations, are also plausible and warrant future research.

CRediT authorship contribution statement

Sara A. Norton: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lauren M. Blaydon:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Megan Niehaus:** Validation, Data curation. **Alex P. Miller:** Writing – review & editing, Methodology. **Patrick L. Hill:** Writing – review & editing, Resources, Funding acquisition. **Thomas F. Oltmanns:** Writing – review & editing, Resources, Funding acquisition. **Ryan Bogdan:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100874.

Data availability

Data will be made available on request.

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