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Positive affect and peripheral inflammatory markers among adults: A narrative review

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ABSTRACT

Background: Previous research suggests that positive affect (PA) may promote health and longevity and that one potential mechanism involves inflammation. However, it remains unclear to what extent PA is associated with specific inflammatory markers and whether such associations are driven by main effects of PA and/or due to PA operating as a stress-buffer.
Methods: The present narrative review incorporates studies ($N = 28$) that have examined the association between PA and peripheral inflammatory markers obtained using venous puncture or dried blood spots. We separate results by whether the study tested direct effects or stress-buffering, and by type of inflammatory marker [including C-reactive protein (CRP), and proinflammatory and anti-inflammatory cytokines], also paying close attention to type of PA assessment (state, aggregated state, or retrospective, the latter involving recall over one to two weeks), and study design (cross-sectional, longitudinal, and experimental).
Results: Limited evidence suggests that studies were more supportive of a stress-buffering association, compared to a relatively direct association. When significant direct associations were observed, results suggested that studies using measures of state/aggregated PA exhibited more consistent associations with inflammatory markers than studies using retrospective PA. When significant, higher PA tended to be associated with lower pro- and anti-inflammatory markers, suggestive of lower overall inflammatory load.
Discussion: Recommendations for the field and future research are discussed, including the value of utilizing state/aggregated PA measures and of examining stress-buffering mechanisms.

1. Introduction

Burgeoning evidence suggests that positive affect (PA) may have important implications for health-relevant outcomes (e.g., depression, cardiovascular disease, mortality), over and above the effects of negative affect (Blazer and Hybels, 2004; Martín-María et al., 2016; Sin, 2016). Biological processes related to immune function may help explain how PA operates to influence these more distal health outcomes, with inflammation playing an important role (Marsland et al., 2007b; Pressman and Cohen, 2005). The present review focuses on two theoretical perspectives that have been posited to explain different pathways by which PA may influence inflammation: the "direct effects hypothesis," which suggests that PA influences regulation of biological systems, and the "stress-buffering hypothesis," which suggests that PA protects against the adverse effects of psychological stress on biological systems (Pressman and Cohen, 2005; Steptoe et al., 2005). The purpose of the present review was to examine the consistency and directionality of direct and stress-buffering associations between PA and inflammatory biomarkers. To provide useful comparisons, we also separate results by type of inflammatory marker, and we highlight the measure of PA used and study design throughout.

1.1. Theoretical assertions regarding PA and health

PA is the subjective experience of emotions, moods, or dispositions that facilitate approaching behaviors and interactions with environments (Fredrickson, 2004). Greater PA has been associated with lower morbidity and mortality (Chida and Steptoe, 2008), lower likelihood of developing cardiovascular disease (Kubzansky and Thurston, 2007), and a lower likelihood of developing viral infections (Cohen et al., 2006).

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With a growing body of literature elucidating the salubrious associations between PA and health outcomes, researchers have begun focusing on the potential mechanisms by which PA may promote health, noting that inflammation may play an important mediating role in this association (Slavish et al., 2019; Steptoe et al., 2005).

The direct effects hypothesis holds that PA directly influences biological processes, such as inflammation, through better regulation of biological systems (Ong et al., 2011). For example, higher PA has been associated with biomarkers that indicate deactivation of the sympathetic nervous system, such as lower epinephrine and norepinephrine (for a review see: Pressman and Cohen, 2005) in ways that suggest that PA may facilitate better regulation of the hypothalamic pituitary adrenal axis (HPA; Kiecolt-Glaser et al., 2002). Dysregulation of the HPA axis is thought to relate to the development of chronic disease, such as cardiovascular disease (Kiecolt-Glaser et al., 2002; McEwen, 1998; Steptoe et al., 2009). Effective regulation of the HPA axis is associated with more adaptive immune function (e.g., lower chronic inflammation, greater antibody responsivity, lower stress responsivity; Ironson et al., 2017; Marsland et al., 2007b; Steptoe et al., 2005), which together may limit the development and/or severity of chronic diseases (Silverman and Sternberg, 2012; Smyth et al., 2013). Specifically related to inflammation, higher PA is therefore theorized to be associated with lower inflammatory markers in the absence of an immune challenge, and to promote a stronger immune response in the presence of an immune challenge, which are both indications of a healthy immune system (Dockray and Steptoe, 2010; Steptoe et al., 2007). Providing some support for the direct effects hypothesis, induction of PA and momentary increases in PA have been associated with more adaptive immune function, including greater responsivity to vaccines and lower responsivity to stress (Costanzo et al., 2004; Steptoe et al., 2007, 2005), as well as evidence of better health, such as lower severity of a variety of acute and chronic illnesses (Pettit et al., 2001) and lower symptomology (e.g., pain; Finan and Garland, 2015). Importantly, implicit in the direct effects hypothesis is the idea that PA should promote better regulation of biological systems irrespective of situational condition (i.e., similar associations under stressful and non-stressful conditions) (Dockray and Steptoe, 2010; Ong, 2010).

In contrast to the direct effects hypothesis, the stress-buffering hypothesis holds that PA moderates associations between stress and health-relevant outcomes. Here we define stress to include external stimuli (stressors) that threaten wellbeing or overwhelm an individuals' ability to respond, appraisals of such stimuli as threatening, and physiological responsivity to stressors (Butler, 1993; Lazarus and Folkman, 1984). According to the stress-buffering theory, higher PA is thought to have an ameliorative influence on associations between stress and health, and thus strong, consistent associations between PA and inflammatory markers may only be evidenced in the presence of an acute stressful or challenging situation (Ong, 2010; Pressman and Cohen, 2005; Pressman et al., 2019), or in the context of chronic life stress (e.g., those with low socioeconomic status). Although stress-buffering is theorized to occur via several pathways (see Pressman et al., 2019 for a review), here we highlight two main processes: that PA buffers against stress by mitigating stress appraisal and therefore augmenting peak responsivity (Blascovich and Tomaka, 1996), and that PA buffers against stress by facilitating faster recovery. In the context of acute stress situations, those with higher PA (or moments with relatively more PA) may be less likely to perceive the stressor as a challenge verses a threat (i.e., mitigation of stress appraisal), and should exhibit lower physiological reactivity (e.g., lower peaks in inflammatory markers) to the stressor, resulting in less frequent and intense stress responses. Over time, this may lead to better health relative to others who have more repeated stressor 'hits' to the system (Smyth et al., 2013). Second, PA may lead to faster recovery from stress (i.e., return to non-stressor baselines), causing less wear and tear (i.e., lower allostatic load) on physiological systems that over time should result in better health outcomes (McEwen, 1998). With respect to inflammation, the stress-buffering hypothesis suggests that higher moments of PA will be associated with lower reactivity and/or faster recovery of inflammatory markers in response to stress. Over time, this altered responsivity should become habitual, such that individuals with higher PA would exhibit weaker associations between stress and inflammatory markers compared with those who have lower PA.

A primary focus of this review is to examine whether the extant literature supports a relatively direct association between PA and inflammation and/or whether it supports a stress-buffering effect. Given the relative dearth of literature examining PA and stress-buffering, the present review will incorporate all studies that can be considered to have stress-buffering regardless of the specific pathways explored (e.g., reactivity vs. recovery).

1.2. Additional factors that may influence associations between PA and inflammatory markers

Several factors likely influence associations between PA and inflammatory markers. We explore two additional considerations in more depth below: PA measurement and type of inflammatory marker.

1.2.1. PA measurement

The term "state" PA is used here to refer to measures of momentary PA (i.e., participants report PA "right now") or reports of very recent PA (i.e., where participants have reported their level of PA "today"). The majority of studies included in this review that assessed state PA did so on a momentary level; because measures of daily PA involve recall as opposed to measures that ask about feelings in the moment, we denote the few instances in the Results/Discussion where state PA was assessed at a daily level. State PA can be used to determine shorter-term fluctuations in PA, which is useful for examining associations between PA and inflammation on fast timescales, such as how moments of greater PA may lead to decreases in inflammatory markers (consistent with direct effects) or how a moment of joy may facilitate faster inflammatory recovery from an acute stressor (stress-buffering). We use the term "retrospective PA" to denote PA recalled over timeframes longer than several days (e.g., PA over the past week or two). PA assessed this way is likely to capture more trait-like processes, or how much PA an individual tends to have in a general sense; such measures are also useful, as they may help illuminate whether people who tend to have more PA on average have lower systemic inflammation or weaker associations between chronic stress and systemic inflammation. Finally, in addition to the terms "state PA" and "retrospective PA" we use the term "aggregated PA" to indicate those studies where state PA measures are aggregated over time to index a longer time frame; like retrospective PA, aggregated PA measures may be more likely to capture more trait-like aspects of PA.

Relatively state-like indicators of psychosocial factors, such as PA, may be more robustly associated with time-variant physiological indicators of health as compared to measures that are recalled over longer periods of time (Wilhelm et al., 2012). On the other hand, measures that represent trait-like tendencies or broad perceptions about the self that are particularly powerful over time (Conner and Barrett, 2012; Pressman et al., 2019). It is also important to separate by measurement type because these different measures of PA may reflect different dimensions of affective experience. Retrospective PA may be more reflective of self-perceptions and peak experiences, whereas state PA captures responses to a specific event or time period (e.g., someone experienced a stressful event 5 min ago, and who thus feels lower happiness than they did earlier the same day) (Conner and Barrett, 2012; Smyth and Stone, 2003; Stone et al., 2000). The aggregate of state PA assessments therefore reflects the average influence of such experience absent of global perceptions of affect.

Both state PA and PA recalled over longer time frames (or aggregated to capture longer time frames) are important for informing psychophysiological pathways described in the direct effect and stress-buffering theories. Each of these theories denotes microlevel processes

(i.e., fast timescale fluctuations in which state PA may link with alterations in inflammatory markers) that, if consistent over longer periods of time, may influence disease pathways (Pressman et al., 2019). Studies exploring state PA provide a feasibility test for microlevel processes. In other words, if moments of PA do not exhibit any association with inflammatory markers, or do not alter linkages between moments of stress and subsequent reactivity or recovery in inflammatory markers, it is unclear how longer-term processes could occur (i.e., these theories suggest that, over time, moments of PA have a cumulative effect on the inflammation leading to lower systemic inflammation). In contrast to the information on microlevel processes that state PA provides, associations between either retrospective PA or aggregated PA and inflammatory markers are thought to provide some indication of the longer-term processes in the direct effects and stress-buffering theories that may lead to a lower likelihood of the development of disease (Pressman et al., 2019).

1.2.2. Type of inflammatory marker

Finally, we distinguish between cytokines that are markers of or which have pro- and anti-inflammatory functions. In the context of acute stress, anti-inflammatory cytokines rise in response to increases in proinflammatory cytokines to regulate/limit inflammation (Elenkov and Chrousos, 2002; Opal and DePalo, 2000); however, perceived stress and chronic stress have been linked with higher levels of both pro- and anti-inflammatory cytokines (Miller et al., 2009; Yamakawa et al., 2009). The present review includes studies that utilized diverse inflammatory markers, which we differentiate in three ways: proinflammatory markers, anti-inflammatory cytokines, and TH-1 cytokines. Many studies utilized proinflammatory markers, including: C-reactive protein (CRP); proinflammatory cytokines interleukin (IL) 6, IL-1β, and tumor necrosis factor α (TNF-α); the proinflammatory chemokine for neutrophils IL-8. Anti-inflammatory cytokines used in the reviewed studies included IL-10 and IL-4. Some of these cytokines have occasionally been categorized as T-helper Type 2 (TH-2) markers, which generate immune responses against extracellular pathogens; however, many have pleiotropic functions, such as IL-6. For the purposes of the present review, these commonly used markers are categorized as either proinflammatory or anti-inflammatory in accordance with how they typically function in the context of psychological stress. We differentiate classic TH-1 cytokines interferon gamma (IFN-ɣ) and IL-2 from other inflammatory markers because they differ in important ways: TH-1 cytokines aid in recruitment and activation of macrophages (which engulf foreign invaders), and promote destruction of localized infections, parasites, and infected cells (Knutson and Disis, 2005; Romagnani, 1992), primarily for intracellular pathogens. To the extent that PA promotes immune function broadly, higher PA may be associated with higher TH-1 cytokines in the presence of an immune challenge; however, given that TH-1 cytokines are typically proinflammatory, higher PA may be associated with lower levels of TH-1 cytokines in the absence of immune challenge.

1.3. Summary of the present review

We present a narrative review examining the extent to which previous research supports direct and stress-buffering associations between PA and inflammatory markers. We first review findings of studies where associations between PA and inflammatory markers are reported, separating our results by whether studies test the direct effects hypothesis or the stress-buffering hypothesis; within these sections we further separate results by type of study (cross-sectional, longitudinal, and experimental), as these likely influence the robustness of the findings, further separating by PA type (retrospective PA, aggregated PA, and state PA). Finally, in a separate section we examine studies by type of inflammatory marker (pro- and anti-inflammatory cytokines, TH-1 cytokines), reporting the consistency and directionality of these associations with PA.

2. Methods

2.1. Criteria for inclusion

In this review we incorporate studies that directly assessed PA and peripheral inflammatory markers among adult samples. Studies involving samples recruited on the basis of specific diseases (e.g., breast cancer patients, depressed adults) were excluded from this review. To enable meaningful comparisons, we limit our review to studies that included circulating peripheral inflammatory markers or measures of stimulated cytokine responses from peripheral blood samples, and we excluded site-specific, salivary, nasal, or central nervous system inflammatory markers.

2.2. Study selection

Four databases (EBSCOhost, Web of Science, PubMed, and PsycINFO) and the reference sections of all papers were used to identify relevant articles for inclusion. Search terms included "positive affect/emotion/mood", "affect/emotion/mood induction", "inflammation/inflammatory", "inoculation", "immune", "cytokine", "TNF-α", "CRP", "IFN- ɣ", and "interleukin". Initial identification yielded 235 unique articles. After examining titles and abstracts as part of initial screening procedures, 64 potential articles were retained for further screening. During the second round of screening procedures, we examined methods and results sections of full-text manuscripts for eligibility. Studies that did not directly measure or manipulate PA or peripheral inflammation were excluded. Additionally, studies that combined measures of PA with other measures (i.e., creating a latent factor of well-being from PA and satisfaction with life, without reporting separately on the unique association with PA) were excluded. Of the 64 full-text studies examined, 28 met inclusion criteria for the present review. These studies were published between 1995 and April 2019.

3. Results and discussion

3.1. Characteristics of included studies

Of the 28 studies incorporated in this review, 15 used a cross-sectional design, four were longitudinal studies, and nine utilized experimental designs. The majority of studies utilized peripheral inflammatory markers that have been frequently assessed in studies linking psychosocial phenomena and inflammation, as reviewed above (e.g., CRP; IL-1β, IL-6, IL-8, TNF-α, IFN-ɣ, IL-10, and IL-4). The function of less commonly assessed inflammatory markers are very briefly described where first noted[1] .

The number of participants in the studies included in this review ranged from 18 to 13,775. Experimental studies tended to have a smaller number of participants (Ns from 18 to 146) than cross-sectional (Ns from 135−3,093) or longitudinal studies (Ns from 71−13,775). Studies with relatively large samples (N > 250) tended to primarily examine CRP and/or IL-6. Most studies reviewed reported at least 50 % of sample comprised of women (16 of 28 studies), with three studies reporting samples comprised of less than 50 % women; seven studies examined PA and inflammation among one gender (five among women only, two among men only), and two did not report gender. Across all studies the age range was 18-91.

3.1.1. Measures

Seventeen studies utilized a retrospective PA measure; the most

[1] Some studies included other biomarkers that are less commonly used in human research related to stress or affect and/or for which the connection to inflammatory function is less clear (e.g., IL-3, IL-12); results for these markers are not incorporated in this review.

frequently used measures for retrospective PA were the Positive and Negative Affect Schedule using the PA subscale (Watson et al., 1988) and a modified version of the Short Form of the Profile of Mood States using the vigor subscale (POMS; Curran et al., 1995). All retrospective measures had instructions asking participants to recall PA over the past week or two weeks. Ten studies utilized a state PA measure (of which two aggregated daily measures, three aggregated momentary measures, and five used an unaggregated state measure). State PA measures included an augmented version of the POMS and other scales based on adjective ratings such as happiness, excitement, and satisfaction. One study examined both aggregated PA and retrospective PA and inflammatory markers (Graham-Engeland et al., 2018).

All studies examined inflammatory markers obtained via venous puncture or dried blood spots. As the majority of studies used venous puncture, we only note in text when studies used dried blood spot. Studies determined inflammatory markers using enzyme-linked immunosorbent assays (ELISA), high sensitivity sandwich immunoassays, or multiplex bead-based assays.

We conducted a quality assessment of each study based on the following items: random or representative sample (0–1), sample size (0–2), utilization of validated/relevant PA measure (0–2), repeated measurement or appropriate manipulation check or control condition (0–1), quality of inflammatory marker handling (0–1), whether biomarker assays were run at least in duplicate (0–1), use of key covariates (age, sex/gender, BMI; 0–2), and reasonable time between PA assessment and blood collection (0–1). If needed information was not reported in the manuscript or easily obtained from a cited paper in the manuscript, a lower score was used. Scores could range from 0−11. Both authors (DRJ, JEG) independently rated each study. Any instance of disagreement on scores was discussed until a consensus was reached. Total scores for quality assessment are provided in Table 1.

Table 1 also provides descriptive information (sample size, age, gender), PA and inflammatory measures, type of study, covariates, time between PA assessment and inflammatory sample collection, and whether each study provides empirical support for the direct or stress-buffering hypothesis. The majority of cross-sectional (90 %) and all longitudinal studies included covariates in their analyses, whereas laboratory studies less consistently used covariates (43 %) but tended to use random assignment. Most studies covaried for (or matched control and experimental groups on) age (85 %), body mass index (BMI; 67 %), gender (59 %), indicators of socioeconomic status (52 %), and health conditions (52 %). Other common covariates included smoking status (48 %), medication use (41 %), and race/ethnicity (22 %).

3.2. Studies examining direct effects

3.2.1. Experimental studies

As noted above, state measures of PA provide a test to the direct effects hypothesis at the microlevel: These studies test whether state fluctuations in PA are linked with changes in inflammatory markers. Only one study met this criteria: Mittwoch-Jaffe and colleagues (1995) conducted an experiment where state PA and inflammatory markers IL-1β, IL-2, IL-6, and TNF-α were taken at baseline and after exposure to a humorous video ($N = 123$). In response to the humorous video, participants reported increased PA, decreased TNF-α, and increased IL-2 compared to baseline. This study provides preliminary support for the hypothesis that state increases in PA can effect changes in inflammatory markers.

Two experimental studies explored whether retrospective PA was associated with stimulated cytokines. Among a small sample of older adults ($N = 18$), in vitro cytokine responses to stimulation by a vaccine and live viruses were examined (using an influenza vaccine to which participants had previously been exposed as well as three novel virus strains to which they had not yet been exposed) (Costanzo et al., 2004). Individuals who reported higher retrospective PA exhibited higher IL-2 and IFN-ɣ responses to stimulation by the three live viruses, and marginally higher stimulated IL-2. Stimulated IL-10 responses were not correlated with retrospective PA. In the second study, associations were examined between retrospective PA and cytokines stimulated in vitro with lipopolysaccharide (LPS; an immunogenic component of gram-negative bacteria; $N = 146$) (Prather et al., 2007). Higher retrospective PA was associated with lower stimulated levels of IL-6 and IL-10, but not stimulated levels of IL-1β and TNF-α. Gender did not moderate associations with stimulated IL-6, but higher retrospective PA was associated with lower stimulated IL-10 only among men. In sum, one study showed that PA was associated with a more robust immune response to several viruses, and one indicated that retrospective PA is associated with lower stimulated pro-inflammatory markers. A more robust response to a vaccine is typically interpreted as evidence of adaptive immune function and lower disease risk (Clem, 2011; Kiecolt-Glaser et al., 1996), as would be chronic or exaggerated patterns of stimulated cytokine response (Marsland et al., 2007a, 2017; Pavlov and Tracey, 2004). Across all experimental studies, results suggest that studies using both retrospective PA and state PA are consistent with expectations for the direct effects hypothesis under controlled laboratory conditions.

3.2.2. Cross-sectional studies

Although cross-sectional studies provide less robust evidence for exploring mechanistic processes, they often allow for larger and more representative samples, and provide important preliminary evidence regarding presence and directionality of associations. Fifteen cross-sectional studies met our inclusion criteria, of these 11 utilized a retrospective measure, three utilized an aggregated PA measure, and one utilized both a retrospective and an aggregated PA measure.

The four cross-sectional studies examining aggregated PA provided fairly consistent support for the direct effects hypothesis. One study (Graham-Engeland et al., 2018) examined whether aggregated PA (momentary PA aggregated over 14 days) was associated with a composite cytokine measure (comprised of IL-1β, IL-6, TNF-α, IL-8, IL-4, IL-10, IFN-γ) and CRP. Aggregated PA was not significantly associated with CRP or the cytokine composite; however, among male participants only, aggregated PA closer in time to the blood draw was associated with lower levels of the cytokine composite. Two studies examined associations between aggregated PA with IL-6 and CRP in relatively large samples. One study ($N = 872$) found that higher aggregated PA (daily PA aggregated on non-stressor days) was associated with lower IL-6, but not CRP (Sin et al., 2015). Another study explored associations in a large sample of civil service employees ($N = 2853$) in the UK (Steptoe et al., 2008). CRP was dichotomized into high and low categories based on criteria for high risk of cardiovascular disease, whereas IL-6 was maintained as a continuous variable. PA was assessed by how frequently participants were very or extremely happy over one day, and was broken down into low (0% of the time), moderate (25–50 % of the time), and high (75–100 % of the time), providing an aggregated measure of PA frequency. Results were only significant for women, and indicated that women in the high aggregated PA category had lower IL-6 and decreased odds of having high CRP (>3 mg/L). The final study ($N = 175$), examined links between aggregated PA (daily PA aggregated over 30 days) and IL-6, CRP, and fibrinogen (Ong et al., 2017). Fibrinogen is a proinflammatory marker that aids in blood coagulation, wound repair, and which helps to regulate the immune system (Davalos and Akassoglou, 2012); higher levels of fibrinogen in the absence of illness or injury are associated with poorer health outcomes, including higher risk of cardiovascular disease and cancer (Davalos and Akassoglou, 2012). Results suggested that aggregated PA was not related to IL-6, CRP, or fibrinogen individually, or to a composite measure of these markers. Together, three of four cross-sectional studies provide some evidence that aggregated PA may be associated with inflammatory markers in ways consistent with the direct effects hypothesis.

In contrast to studies utilizing aggregated PA, in studies examining retrospective PA associations with inflammatory markers yielded far less

Table 1
Studies included in the review and their descriptives.

Study	Population	Measures of Inflammation	Measures of Positive Affect	Type of Study	Covariates	Time between PA and Blood Collection	Quality Assessment Score	Supports direct effect or stress-buffering hypothesis
Andreasson et al., 2013	$N = 347$ 100 % Female Age 45–90	IL-1β, IL-1ra, sIL-1rII, sIL-2 r and IL-6	Retrospective PA: Center for Epidemiological Studies Depression (CES-D) – PA subscale	Cross-sectional	Age, BMI, medication use, smoking	Not reported	8	Direct*
Aschbacher et al., 2012	$N = 35$ 100 % Female Age: 51–75, $M = 61$	IL-1β, IL-6	State PA: Positive Outlook during Stress	Experimental - stress	Age, BMI, caregiver status, AD use, fasting IL-1β baseline	Same day	9	Stress-buffering†
Beydoun et al., 2019	$N = 2580$ 65.33% Female Age: 30–64	CRP, IL-1β, IL-6, IL-10	Retrospective PA: CES-D – PA subscale	Longitudinal	Age, gender, race, education, employment status	Not reported for visit 1; approximately 4.5 years between visit 1 and visit 2	8	(R)†*
Blevins, Sagui, & Bennett, 2016	$N = 3093$ 50.7% Female Age: $M = 29$ ($SD = 1.79$)	CRP – Dried blood spot (DBS)	Retrospective PA: Happiness	Cross-sectional	Age, gender, BMI, race, education, income, tobacco use, exercise, sleep, and anti-inflammatory medication use	Same day	8	Stress-buffering
Costanzo et al., 2004	$N = 18$ 77.8% Female Age: 75–91 $M = 83.9$ ($SD = 54.8$)	(stimulated) IFN-ɣ, IL-2, IL-10	Retrospective PA: Profile of Mood States – Vigor subscale	Experimental - stimulated cytokines	Age, education, marital status, sleep, smoking, caffeine consumption, alcohol consumption, and exercise	Same day	7	Direct*
Friedman et al., 2007	$N = 135$ ($n = 112$ for IL-6, $n = 91$ for sIL6 r) 100 % Female Age: 61–91 $M = 74.5$ ($SD = 7.08$)	IL-6 sIL-6 r	Retrospective PA: Mood and Anxiety Symptom Questionnaire – PA subscale	Cross-sectional	Age, education, income, marital status, depression, health status, anti-inflammatory medication, smoking, alcohol consumption, time between PA and inflammatory data collection	Varied from several weeks to months	7	No association*
Friedman and Ryff (2012)	$N = 998$ 55% Female Age: $M = 58$ ($SD = .40$)	IL-6, CRP	Retrospective PA: Positive and Negative Affect Schedule (PANAS) – PA subscale	Cross-sectional	Age, gender, BMI, race, education, marital status, purpose in life, positive relationships with others, life satisfaction negative affect, chronic conditions, medication use, waist-hip ratio, smoking, alcohol consumption, physical activity, and time between PA and inflammatory data collection	Varied from same day to years	10	Both
Graham-Engeland et al., 2018	$N = 220$ 65 % Female Age: 25–65 $M = 46.21$ ($SD = 11.12$)	CRP, composite score of IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-ɣ	Retrospective PA: happy, alert, enthusiastic, excited, cheerful, relaxed, content, peaceful, calm, satisfied. Aggregated State PA: happy, pleased,	Cross-sectional	Age, gender, BMI, education, chronic conditions, and statin use	Approx. two weeks	10	Retrospective: No association* State: Direct*

(*continued on next page*)

Table 1 (*continued*)

Study	Population	Measures of Inflammation	Measures of Positive Affect	Type of Study	Covariates	Time between PA and Blood Collection	Quality Assessment Score	Supports direct effect or stress-buffering hypothesis
			enjoyment/fun, joyful					
Ironson et al., 2017	$N = 1979$ 58.1% Female Age: 18–96 $M = 51.93$ ($SD = 19.23$)	CRP - DBS	Retrospective PA: PANAS – PA subscale	Cross-sectional	Age, gender, BMI, race/ethnicity, education, depression, smoking, alcohol, and exercise	Not reported	8	Direct*
Janicki-Deverts et al., 2010	$N = 2544$ 55% Female Age: 18–30 at study entry (30+ years ago) $M = 40.20$ ($SD = 3.55$) at year 15	CRP	Retrospective PA: CES-D – PA subscale	Longitudinal	Age, gender, BMI, race, education, depressive symptoms, diagnoses, medications, lipids, triglycerides, glucose, insulin, smoking, alcohol consumption, physical activity, and year 15 CRP	5 years	9	Direct*
Koelsch et al., 2016	$N = 143$ Did not report sex Age: 20–32 $M = 24.8$, 24.9	IL-6	State PA: POMS – vigor subscale	Experimental – affect induction	None; but control and PA condition were balanced with regard to age, gender, BMI, group size	Same day	9	No association*
Kullmann et al., 2012	$N = 18$ 0% Female Age: $M = 26.4$ ($SD = 3.1$)	TNF-α, IL-1ra, IL-6, IL-10	State PA: German Multidimensional Mood Questionnaire	Experimental - immune challenge	None	Same day	6	(R)†*
Lutgendorf et al., 1999	$N = 71$ 100 % Female Age: caregivers $M = 70.9$ ($SE = 8.32$) Movers $M = 79.6$ ($SD = 5.53$) Older controls $M = 76.1$ ($SD = 6.17$) Younger controls $M = 39.9$ ($SD = 9.2$)	IL-6	Retrospective PA: POMS – vigor subscale	Cross-sectional	Age, education, income, marital status, beta blockers, hormone replacement therapy, albumin levels, hours of sleep, cigarettes, alcohol,	Same day	8	Direct
Lutgendorf et al., 2001	$N = 58$ Movers: 60 % Female Non-movers 62 % Females Age: Movers $M = 78.80$ (SD= 5.73) Non-movers $M = 76.85$ ($SD = 7.13$)	IL-6	Retrospective PA: POMS – vigor subscale	Longitudinal	Hormone replacement therapy, beta-blockers	Same day	8	Neither
Mittwoch-Jaffe et al., 1995	$N = 123$ 52 % Female Age: 18–35 $M = 23.4$	IL-1β, IL-2, IL-6, TNF-α	State PA: Mood Adjective Checklist	Experimental – affect induction	No difference between condition on age, gender, or baseline mood	Same day	8	Direct*
Miyamoto et al., 2013	$N = 1426$ 58.49% Female Age: (US) $M = 55.21$ ($SD = 11.79$) (Japan) $M = 54.24$ ($SD = 14.11$)	IL-6	Retrospective PA: Cheerful, in good spirits, extremely happy, calm and peaceful, satisfied, full of life	Cross-sectional	Age, gender, BMI, education, neuroticism, extraversion, smoking, alcohol consumption, and chronic conditions	Varied from same day to years	8	No association*
Morozink et al., 2010	$N = 1028$ 55.00% Female Age: 35–86	IL-6	Retrospective PA: Mood and Anxiety Symptom	Cross-sectional	Age, gender, BMI, education, smoking, alcohol, caffeine	Varied from same day to years	8	Stress-buffering

(*continued on next page*)

Table 1 (*continued*)

Study	Population	Measures of Inflammation	Measures of Positive Affect	Type of Study	Covariates	Time between PA and Blood Collection	Quality Assessment Score	Supports direct effect or stress-buffering hypothesis
	$M = 58.01$ ($SD = 11.64$)		Questionnaire – PA subscale		consumption, physical activity, medication, waist-to-hip ratio, health conditions			
Niles et al., 2018	$N = 13,775$ 59 % Female Age: 30–54 $M = 45.2$ ($SD = 6.2$)	CRP - DBS	Retrospective PA: CES-D – PA subscale	Longitudinal	Age, gender, BMI, cohort, education, medical conditions, exercise, smoking, and alcohol use	Not reported	9	Direct* (R)
Ong et al., 2017	$N = 175$ 54% Female Age: $M = 67$	IL-6, CRP, Fibrinogen	Aggregated State PA: PANAS – PA subscale	Cross-sectional	Age, gender, BMI, neuroticism, extraversion, anti-inflammatory and steroid mediation, and medical conditions	6 months	8	No association*
Prather et al., 2007	$N = 146$ 42.5% Female Age: 30–54 $M = 45.2$ ($SD = 6.2$)	(stimulated) IL-1β, IL-6, IL-10, TNF-α	Retrospective PA: PANAS – PA subscale	Experimental – stimulated cytokines	Age, gender, BMI, race, and white blood cell count	2–4 weeks	8	Direct*
Ryff et al., 2004	$N = 135$ 100 % Female Age: 61–91	sIL-6 r	Retrospective PA: PANAS – PA subscale and Mood and Anxiety Symptom Questionnaire – PA subscale	Cross-sectional	None	Varied from same day to years	4	No association*
Sin et al., 2015	$N = 872$ 57% Female Age: $M = 58$	IL-6, CRP	Aggregated State PA: 13 PA items (e.g., cheerful, calm satisfied, enthusiastic)	Cross-sectional	Age, gender, BMI, race, income, negative affect, chronic conditions, medication use, stressor frequency, and time between PA and inflammatory assessment	Varied from same day to years	10	Both
Steptoe et al., 2008	$N = 2853$ (CRP) $N = 2519$ (IL-6) Did not report sex Age: 50–74	CRP, IL-6	Aggregated State PA: Happy, excited, content	Cross-sectional	Age, gender, BMI, income, ethnicity, employment status, depression, waist-to-hip ratio, smoking, and morning wake time	A few days	8	Direct*
Steptoe et al., 2005	$N = 216$ 46% Female Age: 45–59	Fibrinogen	Aggregated State PA: Happiness	Experimental - stress	Age, gender, BMI, employment grade, smoking, and baseline fibrinogen	A few days	8	Stress-buffering
Sturgeon et al., 2016	N=688 52.3% Female Age: 40–65 $M = 53.91$ ($SD = 7.23$)	IL-6, CRP	Retrospective PA: PANAS – PA subscale	Cross-sectional	None for bivariate correlations	Same day	7	Direct*
Von Känel et al., 2012	$N = 136$ 67.6% Female Age: $M = 74.5$ ($SD = 7.7$)	IL-6, IL-8, TNF-α, IFN-ɣ	Retrospective PA: PANAS – PA subscale	Cross-sectional	Age, gender, BMI, LDL/HDL ratio, systolic BP, diabetes, cardiovascular disease, and smoking	Not reported	7	Stress-buffering
Wolkow et al., 2016	$N = 35$ 14.29% Female Age: $M = 39$ ($SD = 15.51$)	IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-α	State PA: Mood Scale II: Activation and happiness subscales	Experiment - stress	Conditions matched on age, gender, BMI	Same day	7	Stress-buffering†
Wright et al., 2005	$N = 30$ 0% Female Age: 18–30 $M = 22$ ($SD = 3.1$)	IL-6, TNF-α, IL-1ra	State PA: POMS-vigor subscale	Experimental – immune challenge	None but no difference in randomization by age, or physiological measures, or affect	Same day	7	(R)†*

Note. PA = Positive affect. *Stress-buffering hypothesis not examined. †Direct effects hypothesis not examined. (R) Reverse direction examined, with inflammation (or immune challenge) predicting positive affect.

consistent associations that were not robust to the inclusion of covariates. Two of these studies examined associations between retrospective PA and several (>6) different inflammatory markers. In a large sample of women from Sweden ($N = 347$), associations with six inflammatory markers were examined: IL-1β, IL-1 receptor antagonist (IL-1ra), soluble IL-1 receptor II (sIL-1rII), soluble IL-2 receptor (sIL-2 r), and IL-6 (Andreasson et al., 2013). IL-1ra is released from macrophages or monocytes during acute infections (Sirota et al., 2005), whereas sIL-1rII and IL-2 receptor have inflammatory-related functions related to helping regulate the degree to which T-helper cells are activated (Irwin and Rothermundt, 2012). The only significant finding was that lower retrospective PA was associated with having lower and higher numbers of sIL-2 r. The second study examined associations with eight inflammatory markers (IL-1β, IL-6, TNF-α, IL-8, IL-4, IL-10, IFN-γ, CRP) in a sample of midlife adults (N = 220; Graham-Engeland et al., 2018); there were no significant associations.

Six cross-sectional studies examined associations between retrospective PA and inflammatory markers among very large (>500) samples. Two of these examined associations between retrospective PA with CRP via dried blood spot. One study used a national sample of young adults ($N = 3093$) and assessed CRP immediately after participants provided retrospective reports of PA (Blevins et al., 2017); there was no direct association between retrospective PA and CRP. The second study used a nationally representative sample of adults ($N = 1979$) (Ironson et al., 2017). Bivariate correlations indicated that higher retrospective PA was associated with lower CRP. Linear regression analyses indicated that this association held when controlling for demographic variables and for depression; however, in models where BMI and health behaviors were controlled the association was no longer statistically significant. The same pattern of results was found when CRP was dichotomized (±3 mg/L): Those in the low PA group were 1.4 times more likely to have high CRP (>3 mg/L, indicating greater risk for cardiovascular disease) than those with high PA, but these results became non-significant when controlling for BMI and health behaviors.

Three studies with very large sample sizes utilized data from a large national study, the Midlife in the United States Study (MIDUS), using various measures of retrospective PA across available MIDUS samples. In one study, investigators found significant bivariate correlations between retrospective PA and inflammatory markers in a MIDUS sample ($N = 998$), such that those with higher retrospective PA had significantly lower IL-6 and CRP (Friedman and Ryff, 2012). In models that included control variables, associations between retrospective PA and IL-6 were significant only after controlling for negative affect. Another study examined retrospective PA and inflammation in a MIDUS sample and in a smaller sample of Japanese participants ($N = 1426$) (Miyamoto et al., 2013); retrospective PA was not significantly associated with IL-6 in U.S. or Japanese participants, or in the sample overall. Morozink and colleagues (2010) examined associations between retrospective PA and IL-6 ($N = 1028$), but found no significant direct associations. The final study with a large sample also utilized middle-aged adults ($N = 668$). Researchers examined bivariate correlations between retrospective PA with IL-6 and CRP (Sturgeon et al., 2016). Results suggested that higher retrospective PA was associated with lower IL-6 and lower CRP. Covariates were not included except in later models, in which retrospective PA was combined with other measures to create a composite well-being score; analyses using the combined measures are not reviewed here.

Four studies examined associations between retrospective PA in samples of primarily older adults (see Table 1 for age ranges in each study), which could be potentially informative as older adults tend to have higher levels of inflammation and PA could be a potentially useful mechanism to protect against age-related increases in inflammation. In a study of solely older women ($N = 135$), associations were examined between retrospective PA and both IL-6 and soluble IL-6 receptor (sIL-6 r; Friedman et al., 2007), levels of each of which were combined over three time points to obtain more stable measures of these markers. The sIL-6 r is important for activation of inflammatory processes (Jones et al., 2001). There were no significant associations between retrospective PA and either inflammatory marker. Another study of older women also failed to find a significant association between either of two measures of retrospective PA and sIL-6 r (Ryff et al., 2004). Lutgendorf and colleagues (1999) examined inflammatory responses among mostly older female participants ($N = 71$). Higher retrospective PA was significantly associated with lower IL-6. Lastly, one study examined associations with IL-8 and CRP among a sample of older adults (N = 136) that included caregivers and non-caregivers (von Känel et al., 2012). Results indicated that retrospective PA was not associated with IL-8 or CRP (author correspondence). Based on the results of these studies, retrospective PA is not consistently associated with inflammatory markers among older adults, at least when examining direct effects.

In sum, among correlational studies using retrospective PA – which included studies with very large samples, a range of ages, and which were rated fairly highly on our quality assessment (see Table 1) – there seems to be scant evidence that retrospective PA exhibits robust, direct linkages with inflammatory markers. In contrast, although relatively limited in number, the majority of studies examining associations between either state or aggregated PA and inflammatory markers provided some support for the direct effects hypothesis.

3.2.3. Longitudinal studies

Longitudinal studies are important for providing evidence for the longer-term changes inherent in the direct effects hypothesis. Significant associations here would suggest that over time, higher PA (or increases in PA) have a cumulative effect on inflammatory processes resulting in lower systemic inflammation. Two longitudinal studies examined direct associations between PA and CRP, both utilizing retrospective PA assessments, and both provided some support for the direct effects hypothesis. In a population-based sample of older adults in the U.S. ($N = 13,775$), researchers examined associations between retrospective PA and CRP obtained via bloodspot over four years (Niles et al., 2018). Lower retrospective PA at the start of the study predicted increases in CRP four years later. In contrast, CRP at the start of the study was not associated with retrospective PA four years later. Gender differences were examined, but were not significant. Finally, Janicki-Deverts and colleagues (2010) examined associations between retrospective PA and CRP ($N = 2544$) across five years. Lower retrospective PA predicted higher CRP five years later. This effect did not remain significant when controlling for current retrospective PA among European American participants but remained significant among African American participants.

3.2.4. Studies examining reverse directionality

Studies examining reverse directionality provide counter-tests for the causality assumptions in the direct effects theory. This is important because previous work has suggested that the immune system can influence the regulation of affect (Maier and Watkins, 1998; Raison et al., 2006). We found four studies that examined the extent to which inflammatory markers predict changes in PA specifically.

Two of the four studies utilized experimental immune challenges to examine whether increases in inflammation predicted changes in state PA. In the first of these studies, immune responses to LPS were examined in a double-blind experimental study with a small sample ($N = 18$) of male, German participants (Kullmann et al., 2013). Participants came into the lab twice: once where they were injected with a low dose of LPS to induce an inflammatory response and once where they were injected with saline. In each visit, one blood draw was taken just prior to injection, with five blood draws in the subsequent hours following injection

and one 24 h after injection. State PA was examined using an overall PA subscale, as well as two subscales to measure calmness and alertness; these state PA measures were taken prior to each injection, and again three- and six-hours post-injection. In response to the LPS injection, but not the saline, participants exhibited elevated levels of peripheral TNF-α, IL-1ra, IL-6, and IL-10 within one hour and lasting until up to four hours later. When participants were injected with LPS they reported decreased calmness, alertness, and overall PA three hours after injection, and state PA remained significantly decreased six hours post injection. In another study, young men ($N = 30$) were randomly assigned to a typhoid vaccination or a placebo control (Wright et al., 2005) and the associations between state PA and IL-1ra, IL-6, and TNF-α were examined; PA was assessed at baseline and then 1.5, 3, and 6 h post-injection and inflammatory markers were assessed at baseline and 3 h post-injection. Results indicated that state PA declined in the hours following inoculation among those in the vaccine group, but not among those in the placebo group. IL-6 increased in response to the vaccine, but IL-1ra or TNF-α did not. Declines in state PA were not significantly associated with changes in IL-6, IL-1ra, or TNF-α.

The remaining two studies that examined reverse causation utilized a prospective longitudinal design to examine whether changes in inflammation predicted changes in retrospective PA. In a large sample of midlife adults (N = 2580), CRP was used to examine changes in retrospective PA over approximately 4.5 years (Beydoun et al., 2019). In the same study among a smaller subsample of participants ($n = 244–259$; ~60 % African American), the cytokines IL-1β, IL-6, and IL-10 were also assessed. Associations were examined by gender and race; results suggested that IL-10 was negatively associated with retrospective PA among men and African American participants, and that IL-1β was negatively associated with retrospective PA among European American participants, with null associations for IL-6 and CRP. Finally, one previously mentioned study examined bi-directional associations between CRP and retrospective PA. Results from this study suggested that CRP (at time 1) was not predictive of PA four years later; however, retrospective PA (at time 1) was predictive of changes in CRP four years later (Niles et al., 2018).

Together the results of three of four studies examining whether inflammatory markers predict changes in PA provide support for reverse directionality. These results suggest that reverse causality is a possibility, highlighting the need for further studies that can tease apart directional effects. There may be important gender differences in associations: Two of the four studies utilized only male samples (both experimental studies with significant findings), and in the one of the studies with both men and women, results were only significant for men. It would be valuable for additional studies exploring reverse directionality to be conducted with more representative samples.

3.2.5. Summary for direct effects

We identified a total of 20 studies that explored the direct effects hypothesis (with additional studies exploring reverse causality). Results for the five experimental studies and longitudinal studies were consistent with expectations for the direct effects hypothesis, and provided limited evidence for both microlevel and long-term processes. However, there is little consistency among cross-sectional studies, which although somewhat less informative, tended to have larger and more representative samples. Moreover, causality may well go in both directions, as the majority of studies exploring reverse causality found support for the contention that inflammation reduces PA. Finally, third variables potentially accounting for an association between PA and inflammation have not been effectively ruled out; most cross-sectional studies indicated that incorporating important control variables attenuated associations to non-significance. Taken together, support for the direct effects hypothesis is somewhat mixed.

Findings from our review support our speculation that associations between PA and inflammatory markers would vary based on the use of specific PA measures and that such differences may at least partly explain inconsistency among some the aforementioned studies. Of the 12 reviewed cross-sectional studies that examined retrospective PA and inflammatory markers, only two exhibited significant direct associations after potential confounding variables were included as covariates. This is an important finding because the studies reviewed here represent a wide variety of inflammatory markers assessed, with large *N*'s (indicating enough power to detect even small effects), and samples ranging the adult lifespan. In contrast, although fewer in number, three of four studies using aggregated PA measures provided some support for the direct effects hypothesis, even after incorporating important covariates. Retrospective measures may be less robustly linked with inflammation because 1) they are more likely to reflect self-perceptions, peak experiences, and trait characteristics, and 2) there may be longer periods of time between PA assessment and blood draws among studies that use retrospective PA (Conner and Barrett, 2012). Results from the present review do not provide clarity on the first point, but seem to provide some limited support for the latter, in that assessments capturing state affect seems to be more clearly tied to inflammatory markers and studies using state PA (including those that aggregated) tended to have less of a time lag between PA and inflammatory assessment (see Table 1). Bolstering this interpretation, results from a recent study (incorporated in above review) suggested that aggregated state affect assessed closer in time to the blood draw was more robustly associated with inflammatory cytokines than aggregated state affect assessed the week earlier (Graham-Engeland et al., 2018). Hence, the temporal proximity of PA assessment to the blood draw appears to be an important factor for future studies to consider. Future work may benefit from utilizing state measures of PA and aggregating to assess PA over longer time periods.

3.3. Studies assessing stress-buffering

Relative to those testing the direct effects hypothesis, there were somewhat fewer studies that were relevant to testing the stress-buffering hypothesis. Of the 11 studies categorized as testing stress buffering, four were experimental, six were correlational, and one was longitudinal. As noted previously, the stress-buffering hypothesis posits that PA buffers against stress by mitigating stress appraisal and resulting in lower reactivity (Blascovich and Tomaka, 1996), or by facilitating faster physiological recovery. Importantly, most studies reviewed here do not provide a "pure" test of stress-buffering by examining reactivity and recovery, although there are a few exceptions among experimental studies.

3.3.1. Experimental studies

Four experimental studies examined stress-buffering, three of which utilized state PA measures. Aschbacher and colleagues (2012) examined IL-1β and IL-6 reactivity to the Trier Social Stress Test (TSST) among post-menopausal women ($N = 35$). Greater decreases in state PA in response to the TSST were related to greater reactivity in proinflammatory responses to acute stress. Recovery was not examined. In another laboratory-based study ($N = 143$), which used a CO_2 stress test paradigm, researchers assessed the effects of stress on IL-6 and TNF-α (Koelsch et al., 2016). The stress paradigm was associated with increases in IL-6 but not with changes in TNF-α; associations between state PA and TNF-α were therefore not examined. Stressor recovery was assessed, and a randomized music condition was used to increase state PA during recovery. Music was not effective in increasing state PA in all participants; analyses were therefore run using music condition to predict recovery as well as grouping only participants who had increases in state PA. Neither the music condition nor state PA were associated with IL-6 recovery. Gender differences were also explored but were not significant.

One experimental study examined stressful simulated work conditions among firefighters ($N = 35$), in which blood samples as well as two subscales of state PA [activation (e.g., energetic, active) and happiness] were obtained on each day of a three-day study (Wolkow et al., 2016). Blood was drawn four times a day (morning, evening, and twice in the

afternoon) to assess IL-1β, IL-4, IL-6, IL-8, IL-10, and TNF-α. All participants went through the stress condition, which was a physical work circuit that participants completed three times each day after their morning blood draw. This condition was designed to mimic the physical strain and activities of active firefighting. State PA was assessed twice a day (morning and evening). Results indicated that neither subscale of state PA was associated with IL-4 or IL-10. Within-person analyses with the state PA activation subscale suggested that moments of higher activation were associated with increases in IL-6 and IL-1β across days. Sleep deprivation, fatigue, and time strengthened associations. State happiness was generally associated with lower IL-6, higher IL-8, and in some analyses with higher TNF-α (e.g., in the sleep restriction condition). This study provides mixed evidence for stress-reactivity: Results with happiness and IL-6 are consistent with expectations from the stress-buffering hypothesis, whereas feeling more energetic and active were associated with greater immune responsivity during stress in this sample. Importantly, this is the only study reviewed to examine a sustained stress-response (lasting several days). As these authors note, short-term inflammatory marker increases in response to activating stressors can be adaptive (Segerstrom and Miller, 2004). The bulk of theory and empirical work with inflammatory responses suggests that heightened responses and slower recovery to a stressor may represent maladaptive patterns that can confer health risk to the extent that they relate to chronically high levels of inflammation (Glaser and Kiecolt-Glaser, 2005; Marsland et al., 2017).

The one study that examined associations between aggregated PA (momentary PA aggregated over one day) and inflammatory markers did so among a subsample of a larger cohort sample ($N = 216$) from the UK (Steptoe et al., 2005). Results from this study suggested that aggregated PA was not associated with baseline fibrinogen, but was associated with fibrinogen reactivity after two experimental stress tasks (color-word interference and mirror tracing). Consistent with a stress-buffering hypothesis, those in the lowest quintile of aggregated PA exhibited 12 times higher fibrinogen levels after stress compared to those in the highest quintile of aggregated PA. Fibrinogen recovery was not assessed.

Of the four studies that examined whether PA buffered against stress, two provided results consistent with a stress-buffering association, and specifically suggested that higher PA is associated with lower stress-responsivity. The one study examining stress recovery did not find significant associations. In the final study (Wolkow et al., 2016), results were complex, with some indication that activation of PA (specifically high-activation PA) can exhibit a positive association with inflammation under several days of acutely stressful circumstances, but other evidence consistent with a stress-buffering. Although across studies evidence is limited, it may be that PA is more likely to buffer against stress-related inflammatory reactivity than stress-related inflammatory recovery, but more studies are needed exploring both reactivity and recovery as well as longer-term effects.

3.3.2. Correlational studies

Six studies (five using retrospective PA and one using aggregated PA) examined whether PA buffered against the association between factors that could be conceptualized as stressors and inflammatory markers. Importantly, the stressors in the cross-sectional studies reviewed here vary widely, ranging from low education (an indicator of low socioeconomic status and typically associated with poorer health) to living with chronic health conditions or caregiving.

In the only study using daily aggregated PA, data from a MIDUS subsample were used ($N = 872$). Results indicated that individuals who experienced lower declines in aggregated PA on days with stressors (compared to days without stressors) exhibited lower IL-6 and, among women only, lower CRP (Sin et al., 2015).

The remaining studies examined stress-buffering using retrospective assessments, with samples spanning the adult lifespan. In a large, national sample of young adults ($N = 3093$), retrospective PA buffered against the effects of perceived stress such that the positive association between stress and CRP was attenuated for those with higher PA (Blevins et al., 2017). In a study examining associations with IL-8 and CRP among a sample of older adults ($N = 136$) that included caregivers and non-caregivers (von Känel et al., 2012), retrospective PA buffered the association between seeking social support and CRP: Those who had higher social support seeking (potentially indicating increased stress) had higher CRP, but only when retrospective PA was lower. Among samples of midlife adults, two studies have reported that PA may effectively buffer against linkages between stress and inflammation. In one of these studies, PA buffered against associations between chronic conditions and higher IL-6 and CRP: Among those with higher retrospective PA, associations between CRP and health conditions were weaker compared to those with lower retrospective PA (Friedman and Ryff, 2012). In another study of midlife adults, retrospective PA ($N = 1028$) exhibited a buffering effect on the association between education and IL-6 (Morozink et al., 2010): Among those with lower educational attainment, higher retrospective PA was associated with lower levels of IL-6 compared to those with lower retrospective PA. Finally, one study in which inflammatory responses to life stressors (caregiving, relocation) were examined among a sample of female participants ($N = 71$) did not support stress buffering (Lutgendorf et al., 1999). Higher retrospective PA was significantly associated with lower IL-6 across the entire sample; there were no significant group differences by stress group. Importantly, however, the authors note that their stress conditions may not have been strong enough to influence IL-6, as differences in IL-6 in stress and control groups were not statistically significant.

In sum, even after incorporating covariates, five of six correlational studies examining stress-buffering associations exhibited significant results, with higher PA seemingly offering protection against the associations between stress-indicators and inflammation. Here as well there are some important caveats to these findings: First, most of the studies utilized proxies for stress (i.e., low education, seeking social support, living with chronic health conditions, relocation), which do not necessarily equate to stress directly (although they are typically associated with higher stress). Second, given the nature of the assessments, these studies do not provide any evidence for specific mechanisms of stress-buffering (i.e., whether PA protects against reactivity or facilitates stress recovery). Finally, given that only one study examined aggregated PA, we could not examine whether there were differences by PA measurement. Despite these limitations, results from the above studies are largely consistent with the premise that PA protects against stress-relevant associations with inflammatory markers.

3.3.3. Longitudinal studies

One study examined whether retrospective PA buffered against stress-related increases in IL-6. Lutgendorf and colleagues (2001) conducted a study among two groups of older adults who were either voluntarily moving into assisted living facilities (stress group) or who were non-moving controls ($N = 58$). Retrospective PA was not associated with IL-6 in either group before or after moving; similar to their previously reported study, the authors noted that IL-6 did not exhibit strong fluctuations in response to the stress of moving.

3.3.4. Summary for stress-buffering studies

Of the eleven studies that explored associations for stress-buffering, eight were consistent with expectations for the stress-buffering hypothesis. Consistent with long-term processes inherent in the stress-buffering hypothesis, individuals who have higher PA tended to have attenuated associations between stress and inflammation compared to those with lower PA. Moreover, the experimental studies in particular provide evidence for microlevel processes, suggesting that PA may protect against stress-reactivity, although the one study that directly explored inflammatory stress-recovery did not support this association. Perhaps importantly, in all three studies that reported null effects there

were issues with stressors or manipulations: In one study, the PA induction failed to increase PA in approximately 1/3 of participants, and in the other two the stress group did not differ from the non-stress group in inflammatory markers. Thus, together the results from this set of 11 studies provide fairly compelling evidence that PA may indeed buffer against associations between stress and inflammation. Longitudinal studies, however, will be needed for more definitive evidence.

In the reviewed studies, higher levels of either aggregated or retrospective PA were often associated with a diminished association between stress-related psychosocial factors (e.g., perceived stress, lower education) and inflammatory markers; in contrast, among the set of studies examining direct effects, aggregated PA seemed to be more consistently associated with inflammatory markers than retrospective PA measures. It is possible the stress-buffering hypothesis more accurately represents the way in which PA influences inflammation compared to the direct effects hypothesis. Specifically, PA may exert its most ameliorative effects when they are most needed (i.e., in times of stress or difficulty), and be associated with weaker effects at other times (leading to less robust findings with direct associations).

3.4. Results by inflammatory biomarker

Because the inflammatory biomarkers included in this review vary in their functions (Marsland et al., 2007b, 2017) we also report results here by inflammatory marker (irrespective of study design or PA measure) for those markers that were included in at least three of the reviewed studies.

3.4.1. Proinflammatory markers

Proinflammatory markers included IL-1β, IL-6, sIL-6 r, IL-8, TNF-α, fibrinogen, and CRP. Of the six studies that examined whether PA was associated with IL-1β, two reported a significant negative association and one reported a significant positive association. Eleven of 20 studies reported significant associations between PA and IL-6; with the exception of associations with increased high activation PA in one study (Wolkow et al., 2016), all significant associations indicated a negative relation between PA and markers of IL-6, with higher PA being associated with lower IL-6 or PA buffering against associations between stress-indicators and IL-6. However, both studies examining sIL-6 r exhibited null associations. Five studies examined associations between PA and TNF-α. Two of these indicated a significant negative relationship between PA and TNF-α and one indicated a significant (within-person) positive relationship (Wolkow et al., 2016). Seven of 12 studies reported significant associations between PA and CRP. All significant associations indicated that higher PA was associated with lower CRP or buffered against stress-related increases in CRP. As expected, when significant direct linkages between PA and proinflammatory cytokines were noted, the association tended to be negative.

3.4.2. Anti-inflammatory markers

Only seven studies examined associations between PA and anti-inflammatory cytokines (one study used a composite that combined pro- and anti-inflammatory markers, results of which were not incorporated in this section). Anti-inflammatory cytokines in the reviewed studies were IL-1ra, IL-4, and IL-10. Three studies examined associations between PA and IL-1ra but only one reported a significant (negative) association (Kullmann et al., 2013). Of the five studies examining associations between PA and IL-10 three studies exhibited a significant inverse relationship with PA. We had no strong expectations regarding the directionality with which PA would relate to anti-inflammatory markers. Our review revealed that when there was a direct association between PA and anti-inflammatory cytokines, similar to associations with proinflammatory cytokines these also tended to be negative. This is not surprising, as anti-inflammatory cytokines tend to rise and fall in conjunction with pro-inflammatory cytokines to regulate immunity (Prather et al., 2007). The results of these studies broadly suggest that higher PA is associated with lower inflammatory profiles.

3.4.3. TH-1 inflammatory cytokines

Three studies examined associations between PA and TH-1 associated cytokines. One study indicated that higher PA was significantly associated with higher levels of peripheral IL-2. Another study indicated a curvilinear relationship, with higher PA being associated with higher and lower soluble IL-2 receptor. Finally, one study indicated that higher PA was associated with higher stimulated IFN-ɣ. Together, limited evidence may support a positive association between PA and TH-1 cytokines. TH-1 cytokines are proinflammatory cytokines that are important for cell-mediated immunity (i.e., the destruction of bacteria, viruses, and tumor cells). That higher PA was associated with TH-1 markers more consistently than with classical proinflammatory markers suggests that PA may have important health effects for intracellular illness and disease. However, with only three studies examining TH-1 markers, more research is needed before definitive conclusions can be made.

3.5. Recommended future directions

Overall, findings from the present review suggest that 1) stress-buffering is a likely mechanism by which PA is associated with inflammation, 2) state and aggregated state PA is more robustly linked with inflammatory markers compared to retrospective PA when examining direct effects, and 3) PA is broadly associated with decreased pro- and anti-inflammatory cytokines. However, it is clear from our review that a substantial amount of work needs to be done to further establish mechanistic associations between PA and inflammation. There are several areas in which future research could improve understanding of these complex associations. First, few studies clearly delineated whether PA influences stress-related inflammatory reactivity, stress-related inflammatory recovery, or both. Additionally, more research is needed to examine whether PA exhibits a stress-buffering effect on certain classes of inflammatory markers; for example, in the present review we found that very few studies examined PA as a buffer of the effects of stress on anti-inflammatory or TH-1 cytokines. Future studies with a stress-buffering lens that address the two aforementioned issues will help clarify mechanistic routes by which higher PA relates to lower disease risk. Another related direction for future work is the examination of circumstances under which PA can influence the inflammatory cascade that occurs in response to an acute stressor. Limited work suggests that PA may be implicated in the gene expression of particular cytokines during acute stress (McInnis et al., 2015), that PA may influence the inflammatory response when an individual is exposed to various antigens (Costanzo et al., 2004; Prather et al., 2007), and that these associations between PA and inflammation may be different following several days of stress or fatigue (Wolkow et al., 2016). More work is needed to ascertain whether PA is associated with increases or decreases in particular inflammatory markers under different conditions (e.g., acute vs. prolonged stress), and to determine the mechanisms through which PA may influence such inflammatory change.

Both PA and cytokine levels can change over relatively short time windows, and the associations between PA and inflammatory markers appear to become weaker with increasing time between assessments (Graham-Engeland et al., 2018). Future research seeking to better establish linkages between PA and inflammatory cytokines should prioritize measures of PA that are momentary (e.g., how happy do you feel right now) or at least daily (e.g., how happy were you today) and which can be aggregated to appropriate time windows to maximize co-variation with fluctuations in inflammatory markers, ensuring that these measures are both contextually and temporally linked. Alternatively, if PA ratings are obtained over a certain time period (e.g., a week) and aggregated, inflammatory measures might be obtained at either end of that time period to better capture inflammation that maps on to the same period of time, and to enable examination of reverse causality. When neither of these options are possible, studies should explicitly

determine and account for the time difference between PA assessment and blood draw in analyses, particularly if it varies across participants.

Studies linking affect and inflammation have varied widely in their inclusion of covariates. The use of key covariates when linking PA with inflammatory markers are important to ensure that critical confounding variables (e.g., age, gender, and BMI) do not explain the relationship between PA and inflammation. Indeed, based on studies in the present review, it seems particularly important that health behaviors such as substance use (i.e., smoking, alcohol consumption) and physical activity, and health conditions are incorporated as covariates in addition to BMI, age, gender (Friedman and Ryff, 2012; Ironson et al., 2017). Conversely, it is possible to over-control for factors that may relate to the mechanistic process(es) by which PA links to inflammation (O'Connor et al., 2009). We recommend utilization of a model-building approach, to better examine whether covariates help explain the connection(s) between PA and inflammation.

3.6. Limitations

There are several limitations to what the present review could accomplish. First, it is important to note that the utilization of state PA was somewhat confounded with other methodological factors. For example, studies examining certain types of inflammatory markers were more likely to use state PA: IL-1β was more frequently assessed in studies utilizing state PA, and fibrinogen was only assessed in studies using aggregated state PA. Thus, IL-1β and fibrinogen are underrepresented in studies examining retrospective PA. Additionally, laboratory studies were more likely to use state PA. These factors and other methodological differences between studies suggest that methodology and measurement may be confounded, limiting our ability to draw firm conclusions.

Second, it is important to highlight that causality between PA and inflammation was not clear from the majority of studies reviewed. The theoretical framework we have utilized for direct associations envisions PA as a predictor of lower inflammation, and indeed, approximately half of studies reviewed here support this association. Studies utilizing retrospective measures of PA seem to account for some of the discrepancy in direct associations between PA and inflammation. However, it is also possible that associations move in the opposite direction as was being tested in these studies (i.e., inflammatory markers may influence changes in PA) or that a third variable (e.g., depression, socioeconomic status) is responsible for associations between PA and inflammation. Clearly, more work is needed to determine causality.

Third, among studies that employed a stress-buffering lens, conceptualizations of stress differed across studies. Importantly, failures to elicit a stress-response or a PA response seemed to account for the non-significant results seen in the stress-buffering conditions; however, this too limits conclusions that can be drawn from the extant literature. Perhaps most importantly, few studies explored a "true" stress-buffering association, where a baseline of stress is measured within-person and reactivity/recovery were also subsequently measured to capture a more complete picture of the inflammatory stress-response. More studies with validated stress-paradigms, particularly those that are longitudinal, are needed to better explore stress-buffering. Despite these limitations in stress-buffering, all studies that had effective stress-buffering or PA manipulation exhibited significant associations consistent with expectations from the stress-buffering hypothesis, suggesting that exploration of stress-buffering is a promising avenue for future studies.

Finally, as highlighted by our quality assessment, studies reviewed here had highly varying N's, covariates, and study designs, and gender differences were not consistently tested for or incorporated in analyses despite clear evidence for gender/sex differences in levels of circulating inflammatory markers. Moreover, numerous studies conducted a number of statistical analyses without correction. These issues may indicate there are high Type 1 error rates and/or publishing bias (toward publication of significant findings), which could influence conclusions drawn from the present review. Given these possibilities and the fairly small number of relevant studies to date, all results discussed here should be interpreted with caution until a larger number of studies are conducted to support a meta-analysis.

3.7. Concluding remarks

We conducted a review of 28 studies examining associations between PA and inflammatory markers and the extent to which findings suggest relatively direct associations with PA or a stress-buffering role of PA. We also considered whether associations differed based on PA measurement (i.e., based on state, aggregated, or retrospective) or type of inflammatory marker (i.e., pro or anti-inflammatory, TH-1 cytokines). The studies reviewed here provide fairly robust support for PA serving as a buffer of the effects of psychological stress, with evidence from eight of 11 studies (six cross-sectional, one longitudinal, and four experimental studies) that PA can weaken the associations between stress (and stress-related phenomena) and circulating inflammatory markers. Moreover, among studies showing significant associations, results overall suggest that PA is associated with lower peripheral levels of pro and anti-inflammatory markers. Finally, consistent with assertions that momentary measures may be more reliably associated with physiological markers of health than retrospective measures (Conner and Barrett, 2012), state PA measures or measures aggregated from state PA were generally more consistently associated with inflammatory markers than retrospective PA measures among studies examining direct effects. In contrast, both retrospective PA and aggregated/state PA were shown to effectively buffer associations between stress measures and inflammatory markers. The findings of this review suggest that future research should utilize momentary or daily measures of PA when possible and/or focus on stress-buffering mechanisms as one way that PA may relate to lower disease risk.

Declaration of Competing Interest

The authors report no declarations of interest.

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