Inflammation Through a Psychoneuroimmunological Lens

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19.1 Psychoneuroimmunology

Psychoneuroimmunology (PNI) is a field in which researchers investigate the intersections among behavior, the nervous system, and the immune system. Its development over the past 35 years followed the realization that the immune system does not function in isolation [1, 2]. The initial focus on biological mechanisms encouraged the use of animal models to uncover pathways through which the brain and behavior affect immune activity. Once biological pathways were established, researchers started replicating similar results in humans with broad applications in areas such as infectious diseases, cardiovascular disease, autoimmunity, and cancer. Today, the transdisciplinary field of PNI continues to unravel the complex connections among behavior, immune function, and health.

In this chapter, we use a PNI lens to understand and describe the complex influences of biology and psychology on inflammation. Inflammation is an underlying etiological factor in many chronic diseases. A brief description of brain–immune communication is first introduced as background, followed by a summary of inflammation's effect on health. The biological, psychological, and psychosocial influences on inflammation are then discussed, followed by a review of inflammation and cellular aging.

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19.2 Neuroendocrine–Immune Communication

The two major stress systems include the sympathetic–adrenal–medullary (SAM) axis and the hypothalamic–pituitary–adrenal (HPA) axis. Both systems influence inflammation and affect immune cells through adrenergic and glucocorticoid receptors; the end products of SAM and HPA axes can modulate immune functioning [3]. Of note, neuroimmune communication is not limited to these two pathways; however, an in-depth review of the bidirectional communications between the nervous and immune systems is beyond the scope of this chapter. There are several thorough reviews that address the ways in which neuroimmune communications occur and the observed effects [4–6].

The SAM axis connects the brain directly to the adrenal medulla via sympathetic innervations. Upon stimulation, the adrenal medulla releases catecholamines, epinephrine and norepinephrine. Although catecholamines have short half-lives and are metabolized quickly, they can regulate many facets of the immune system [4]. Therefore, chronic sympathetic activation can lead to immune dysregulation.

Epinephrine increases interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) production during stress [6]. In addition, norepinephrine promotes nuclear factor-kappa B (NF-κB) activation [7]. NF-κB is a transcription factor that regulates the gene expression of several proinflammatory mediators, such as IL-6 and IL-8 [8, 9]. NF-κB activation increases the gene expression of inflammatory mediators, which in turn enhances inflammation [7]. Therefore, epinephrine and norepinephrine can induce proinflammatory cytokine production.

Although inherently slower than the SAM axis, the HPA axis provides a more sustained response following activation. It begins with the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary into the blood stream. In turn, ACTH stimulates the adrenal cortex, its target organ, to produce cortisol, a glucocorticoid [10]. A negative feedback loop regulates HPA axis activation. Cortisol binds to glucocorticoid receptors in the hippocampus which inhibit the production of CRH and ACTH from the hypothalamus and anterior pituitary, respectively [11]. Other neuroendocrine hormones influence the HPA axis including androgens, estrogens, and posterior pituitary hormones, vasopressin and oxytocin [12–14].

Cortisol can inhibit immune cell activity by binding to glucocorticoid receptors; this process inhibits activation and release of proinflammatory cytokines [15, 16]. However, chronic stress can lead to hippocampal damage and HPA axis dysregulation resulting in increased cortisol production [17]. Chronically elevated cortisol can induce glucocorticoid insensitivity where immune cells downregulate the expression of glucocorticoid receptors [18, 19]. As a result, inflammation is increased due to unregulated immune cells producing proinflammatory cytokines [20].

Neuroendocrine–immune communication is not unidirectional. The immune system communicates with the brain via cytokines. For example, IL-1 receptors are located throughout the brain, especially in the hypothalamus. In turn, IL-1 can stimulate CRH secretion from the hypothalamus, leading to increased HPA axis activity [21]. Peripheral cytokines induce sickness behavior, behavioral changes that are associated with fever, decreased energy, decreased appetite, and changes in sleep [22]. Proinflammatory cytokines can access the brain through a variety of pathways including the leaky regions in the blood–brain barrier (e.g., circumventricular organs) and cytokine-specific transport molecules expressed on brain endothelium [5]. In addition, the vagus nerve detects cytokine levels in the periphery and relays this information to the brain via afferent fibers [23, 24]. This bidirectional communication not only allows an integrated response to occur, but also increases the opportunity for dysregulation when one system is disrupted (Fig. 19.1).

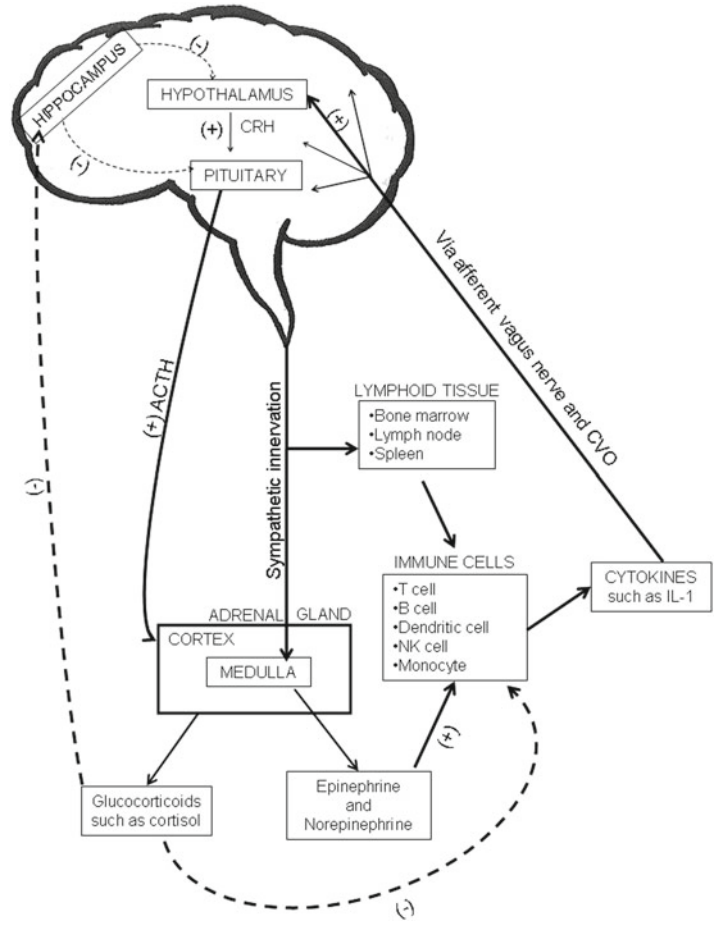

Fig. 19.1 Neuroendocrine–immune bidirectional communication. Hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system influence the immune cells through glucocorticoid and adrenergic receptors. Immune cells can communicate with the brain via peripheral cytokine levels surveyed by the circumventricular organs and the afferent vagus nerve. *CRH* corticotropin-releasing hormone, *ACTH* adrenocorticotropic hormone, *NK* natural killer, *IL* interleukin, *CVO* circumventricular organs

19.3 Health Consequences of Inflammation

Inflammation is an immune response to infection or injury that aids in the removal of foreign pathogens and promotes wound healing. Acute inflammation is beneficial; however, chronic low-grade inflammation is harmful. Chronically high levels of inflammation are found in a number of age-related diseases including cardiovascular disease and cancer [25–28].

Inflammation can be measured by assessing serum or plasma levels of acute-phase proteins and proinflammatory cytokines. C-reactive protein (CRP) is the most commonly studied acute-phase protein; acute infections and tissue damage increase IL-6 levels that in turn induce liver production of CRP [29]. CRP can bind to foreign or damaged cells and lead to cell destruction. Many cells throughout the body including immune cells, adipocytes (fat cells), and damaged cells, produce proinflammatory cytokines such as IL-6 and TNF-α that then recruit and stimulate additional immune cells to clear and repair tissue. In addition, IL-6, TNF-α, and IL-1 levels follow a diurnal rhythm such that peak levels occur during the early night and reach a nadir in the morning [30, 31]. CRP, however, does not appear to vary across the day [32].

Outside of acute infection and tissue injury, CRP is considered clinically relevant as a nonspecific biomarker of inflammation; minor elevations have been linked to cardiovascular disease risk [33]. For example, individuals with CRP

greater than 3 mg/L are at higher risk for developing cardiovascular disease. Unlike CRP, there are no clinically relevant standards for proinflammatory cytokines. Therefore, a typical research strategy is to compare individuals with higher proinflammatory cytokines to those individuals with lower levels or unhealthy patient populations with healthy controls. In addition, researchers may also investigate within-person changes in proinflammatory cytokine levels following a study manipulation such as an intervention or laboratory stressor.

Individuals who have higher levels of inflammation are at greater risk for many diseases including cancer, cardiovascular disease, type 2 diabetes, Alzheimer's disease, osteoporosis, rheumatoid arthritis, and periodontal disease. Elevated inflammation is associated with greater all-cause mortality risk [34]. We briefly review how inflammation contributes to cardiovascular disease, cancer, and type 2 diabetes, three diseases that account for the majority of deaths in developed countries [35].

In the case of cardiovascular disease, proinflammatory cytokines facilitate early atherogenesis and clinical vascular events [36]. Inflammation contributes to atherosclerosis by reducing vascular endothelial cells' capacity to resist leukocyte (white blood cell) adhesion. When leukocytes adhere to vascular endothelial cells, they proliferate, and enhance cytokine production. Elevated inflammation has been implicated in the onset of clinical vascular events because they weaken fibrous caps. Weak fibrous caps are more likely to rupture leading to a heart attack or stroke [37].

Inflammation is also linked to cancer incidence and progression [38]. Chronic inflammation is a contributing factor in at least 15% of all cancers and also influences tumor survival, proliferation, invasion, angiogenesis, and metastases [38–40]. When proinflammatory cytokines enter tumor cells, they promote uncontrolled growth and subsequent metastasis. Furthermore, when macrophages are activated during the inflammatory response, they release many different cancer-promoting messengers including growth and angiogenic factors, proteases, and reactive oxygen species [40].

Individuals with type 2 diabetes are insulin-resistant, which means they either cannot produce enough insulin or the body cannot use the insulin adequately. Inflammatory cytokines can mediate insulin resistance. For example, elevated inflammation impairs blood glucose control by suppressing insulin signal transduction [41, 42]. Furthermore, TNF-α is the major proinflammatory cytokine implicated in this process [43].

In sum, elevated inflammation has been linked to disease progression. Yet, it is unknown whether higher cytokine levels cause the disease, or if the disease results in greater proinflammatory cytokine production. However, we do know several factors that influence inflammation. The following sections describe how biology and behavior affect proinflammatory mediators.

19.4 Biological Influences on Inflammation

19.4.1 Age

Proinflammatory cytokine levels rise with age and have known ties to a number of age-related illnesses [27, 44]. Circulating IL-6, soluble IL-6 receptor (sIL-6r), TNF-α, soluble TNF receptor II (sTNFR-II), and IL-1 receptor antagonist (IL-1ra) increase with age [44–47]. A recent review describes the relationship between age and inflammation as linear, but evidence has not established the age when the relationship can first be detected [48]. For example, in studies with middle-age and older adults (≥40 years old), inflammation increases with age [45, 46, 49, 50]. However, among young adults (≤30 years old), the linear relationship between inflammation and age does not appear consistently [46, 49], suggesting that young adults' health behaviors may have more salient influences on inflammation than age.

Epidemiological studies in healthy older adults indicate a twofold higher risk of all-cause mortality in those who had IL-6 levels in the highest quartile compared to those in the lowest IL-6 quartile, independent of known health risks [34]. When compared to those in the lowest tertile, elderly individuals whose IL-6 levels were within

the highest tertile range were nearly 2 times more likely to develop mobility-related disability, and 1.5 times more likely to develop additional disability related to activities of daily living [51].

Interleukin-6 promotes CRP production by the liver [52]. In a group of healthy participants, older adults [75.4 ± 6.8 years (±SD)] had higher CRP than young adults [31.6 ± 7.7 years (±SD)] [53]. In several large population-based studies, CRP increased as men and women aged, even after controlling for possible pre-existing conditions and sub-acute illnesses such as cardiovascular risk factors and disease [46, 49, 54]. High CRP levels are clinically significant; particularly when predicting cardiovascular disease risk [29, 55, 56]. In a recent meta-analysis, individuals with CRP levels >3.0 mg/L were 1.54 times more likely to experience a cardiovascular event than those with <1.0 mg/L CRP [57].

19.4.2 Obesity

Obesity is characterized by elevated circulating proinflammatory cytokines; hence, obese individuals experience a state of chronic inflammation. In epidemiological studies, obese individuals had higher CRP compared to those not obese, even after controlling for negative health behaviors and disease status [58]. Similarly, obese individuals had higher CRP per unit increase in weight, body mass index (BMI), and waist circumference compared to normal weight individuals over a 10-year span [59]. Circulating IL-6, as well as IL-6 produced from abdominal adipose tissue, increases with adiposity [60]. In addition, IL-6 released from abdominal adipose tissue accounts for an estimated 30% of systemic IL-6 in healthy, overweight subjects [60]. Among premenopausal women, obese women had higher IL-6 levels before and after public speaking stress compared to non-obese women [61].

Obesity-induced inflammation has been linked to the development of insulin resistance. Increased obesity was associated with greater CRP, IL-6, and TNF-α. Higher CRP was also related to insulin resistance, suggesting that elevated inflammation may underlie the progression of metabolic syndromes including type 2 diabetes [62]. In participants with obesity-related insulin resistance, abdominal adipose tissue expression of TNF-α and plasma IL-6 were elevated compared to insulin-sensitive participants [63]. Interestingly, the two groups were matched for BMI, suggesting that being insulin-resistant elevates inflammation beyond that observed in obese individuals.

Diseases with an inflammatory component can be exacerbated by insulin resistance. For example, hepatitis-C-infected patients with comorbid type 2 diabetes had higher TNF-α levels than patients without type 2 diabetes [64]. In addition, TNF-α inhibitors significantly improved insulin sensitivity in patients with rheumatoid arthritis [65]. The infusion of TNF-α lowered insulin-mediated glucose uptake and induced IL-18 gene expression in human muscle tissue [66], which demonstrates the relationship between these two inflammatory mediators and their effects on insulin resistance.

Weight loss lowers inflammation. For example, a diet-induced weight loss intervention reduced circulating levels of CRP, IL-6, and sTNFR-1 in a sample of older adults, regardless of physical activity, suggesting that weight reduction is independently associated with reduced proinflammatory cytokines [67]. Serum TNF-α levels in obese individuals fell ~25% after an average weight loss of 12 kg [68]. Two years after a diet and exercise intervention in obese women, the treatment group had lower IL-6, IL-18, and CRP levels related to weight loss than obese women in the control group [69]. In another study, weight loss reduced plasma IL-18 and increased insulin sensitivity [70].

Measures of relative fat mass composition may partially account for the relationship between physical activity and inflammation. For instance, more physical activity resulted in lower IL-6, CRP, and sTNFR than less physical activity; however, when adjustments were made for BMI and leptin levels, physical activity no longer was related to decreased inflammation [71]. During a 3-year follow-up period, increased low-grade inflammation was

associated with greater adiposity, but not physical fitness [72]. Therefore, although physical activity is associated with lower inflammation, this relationship may result from less obesity in physically active people.

19.4.3 Sex

Sexual dimorphic immune responses can be readily observed in human populations. For example, women are more like to suffer from an autoimmune disease; however, men are disproportionately affected by Parkinson's disease and early-onset cardiovascular disease [73, 74]. Gonadal hormones (e.g., estrogen, progesterone, and testosterone) may partially account for the differences observed between males and females. Androgen and estrogen receptors are present on immature immune cells in the thymus and bone marrow [75–77]. However, sex differences in gonadal hormones do not fully account for disparities in circulating inflammatory markers between males and females.

Levels of most inflammatory markers do not differ consistently between sexes, although CRP levels are one exception. In large population-based studies, females have higher CRP levels than males [78–80]. During the follicular phase of the menstrual cycle, women had lower levels of CRP compared to those in the luteal phase [81]. Post-menopausal women have higher CRP than premenopausal women [82]. In addition, women using oral contraceptives or hormone replacement therapy (HRT) have increased CRP levels compared to age-matched women not taking hormones [49, 83–87].

Unlike the reliable CRP difference, proinflammatory cytokines such as IL-6 and TNF-α are not always different between the two sexes [88, 89]. It remains unclear whether menstrual cycle phase and menopausal status impact proinflammatory cytokines. The follicular phase may be associated with higher IL-6 levels compared to the luteal phase [90]. However, several studies suggest that inflammation is greater during the luteal phase compared to the follicular phase [91–93]. Neither menstrual cycle phase nor oral contraceptive use affects proinflammatory cytokine levels [87, 94–96]. The use of HRT inconsistently affects proinflammatory cytokines, with studies showing decreases, increases, and no change [83, 84, 97, 98]. These discrepant findings may be due to relatively small sample size; the majority of the proinflammatory cytokine studies include 68 women or less.

19.5 Psychological Influences on Inflammation

19.5.1 Depression

Patients with inflammatory-related diseases including cardiovascular disease and cancer have higher rates of depression compared to healthy individuals [99, 100]. Both syndromal depression and depressive symptoms are associated with heightened levels of proinflammatory mediators including IL-1, IL-6, and CRP [101–105]. Additionally, depression severity and inflammation appear to have a dose–response relationship; as depressive symptoms worsen, inflammatory markers increase [104, 106]. While these findings demonstrate an association between depression and circulating levels of proinflammatory cytokines, it is important to consider factors that influence inflammation and covary with depression including antidepressant use, sex, BMI, and comorbid symptoms of anxiety [48, 107].

Not only do depressed people have higher inflammatory levels, they also have a greater inflammatory response to stress. For example, compared to nondepressed males, those with major depression show greater IL-6 and NF-κB activity in response to acute psychosocial stress [108]. Clinically depressed individuals also display decreased sensitivity to the anti-inflammatory properties of glucocorticoids, resulting in greater production of IL-6 and TNF-α compared to their nondepressed counterparts [109, 110]. Thus, excessive NF-κB activity and decreased responsiveness to glucocorticoids may enhance and

sustain the production of proinflammatory cytokines in individuals with depression.

Growing evidence suggests that the relationship between depression and inflammation is bidirectional. Administration of interferon-alpha and other cytokine inducers produces depression-like symptoms including low mood, fatigue, and psychomotor slowing in otherwise healthy volunteers [111, 112]. Cytokines appear to influence the production and metabolism of mood-relevant neurotransmitters such as serotonin, dopamine, and norepinephrine [113]. Moreover, clinically depressed individuals who receive anti-inflammatory medication in addition to antidepressants show greater symptomatic reduction than those who receive a combination of antidepressant and placebo [114, 115]. Elevated inflammation affects not only physical health, but also emotional well-being, including anxiety.

19.5.2 Anxiety

Laboratory-based and cross-sectional studies in healthy and patient populations have been used to investigate the relationship between anxiety and inflammation. In the laboratory setting, stress-induced increases in anxiety and anger enhanced IL-6 production following stress [116]. These associations varied by sex; for women, anxiety was more strongly associated with IL-6 responses, while anger in men was related to IL-6 production [116]. Administration of endotoxin, a substance used to mimic an actual infection, increased anxiety as well as circulating levels of TNF-α, IL-6, and IL-1ra [111].

Cross-sectional studies indicate that anxiety can influence inflammation outside the laboratory. During an examination, anxious medical students produced more proinflammatory interferon-gamma (IFN-γ) and less anti-inflammatory IL-10 and IL-4 compared to non-anxious medical students [117]. More anxious adults had higher CRP, IL-6, and TNF-α than less anxious ones [118].

Anxiety may exacerbate inflammatory responses in people with allergies. In patients with allergic rhinitis (AR), anxiety enhanced the effects of stress on late-phase responses assessed 24-h after a skin prick test (SPT), and was associated with higher IL-6 production [119]. Therefore, continued inflammation that occurs during late-phase allergic responses may "prime" hyperresponsiveness to irritant triggers and other allergens, especially in anxious AR patients. In addition, anxious AR patients' lymphocytes had greater Concanavalin A (ConA)-stimulated IL-6 production compared to those who were not anxious [119].

Chronically ill individuals may be especially susceptible to anxiety's effect on inflammation. For instance, leukocytes from anxious hemodialysis (HD) patients produced significantly higher in vitro levels of IL-6 compared to less anxious HD patients [120]. This anxiety-related increase within the HD patient group was over and above the already observed higher inflammation in the HD patients compared to healthy controls [120], suggesting that anxiety may have an additive effect on inflammation in patient populations.

19.6 Psychosocial Influences on Inflammation

19.6.1 Socioeconomic Status

Epidemiological data demonstrate consistent and striking effects of socioeconomic status (SES) on health outcomes [121, 122]. Measures of SES often include income, education, and occupational prestige as the three main components. Lower SES individuals have higher rates of all-cause mortality and a lower life expectancy [123–125]. In particular, one estimate indicates that those with a lower SES have a lifespan 4.5 years shorter than their higher SES counterparts [126]. Furthermore, health disparities increase with each step down the SES ladder [122].

An individual's SES can shape their life course and lead to a number of lifestyle choices, many of which may contribute to the observed association between SES and health. For instance, individuals with low SES are more likely to engage in behaviors such as smoking, excessive alcohol use, reduced physical activity,

and they are more likely to experience stress and depression, all of which can negatively impact health [127]. Despite these associations, the relationship between low SES and mortality persists even when these factors are statistically controlled [128].

Heightened inflammation may provide one link between low SES and poor health outcomes. In fact, a number of acute and chronic medical conditions are associated with both elevated levels of inflammatory markers and low SES. Compared to higher SES individuals, lower SES individuals have higher IL-6, TNF-α, and CRP [55, 129–132]. The individual components of most composite SES measures, such as income and education, show similar negative associations with proinflammatory cytokines [133, 134]. While informative, these associations do not explain the mechanisms through which low SES promotes inflammation and, by proxy, poor health outcomes.

Different inflammatory responses to psychological stress may partly account for health disparities between SES groups. Compared to high SES individuals, lower SES individuals show greater increases in IL-6 and CRP that persist longer in response to acute mental stress [135, 136]. Thus, lower SES individuals tend to have maladaptive responses to stress, an attribute which may play a role in maintaining higher levels of inflammation. While the pathways through which low SES individuals develop negative health outcomes remains unclear, increased inflammation represents an attractive possibility.

19.6.2 Social Support

Close relationships have clear ties to better health and reduced inflammation may account for these associations. Social support refers to the degree that one believes that support would be available if and when it is needed [137]. In one study, older women who had more satisfying interpersonal relationships had lower IL-6 compared to those who had less satisfying relationships [138]. In another study, women with ovarian cancer who reported greater social support had lower circulating IL-6 levels compared to women who reported less social support [139]. Furthermore, gynecologic cancer survivors who sought more support at diagnosis had lower circulating IL-6 one year later compared to those who sought less support [140].

19.6.3 Marriage

Married individuals' mortality rates are lower than those of their unmarried counterparts [141]. Inflammation may be one possible mechanism for these findings. In a population-based study of community-dwelling older adults, being married was associated with reduced CRP for both sexes; these effects were particularly pronounced in men [142]. The absolute magnitude of the risk reduction for married men was equivalent to being a nonsmoker, having normal blood pressure, and having a healthy BMI [142].

While marriage typically has positive health benefits, marital quality has important health implications [143]. Marital interaction studies demonstrate the relationship between marital quality and immune function. Hostile marital interactions have particularly important negative physiological consequences. Both younger and older couples who were more hostile to their spouse during marital problem discussions produced more epinephrine, norepinephrine, and ACTH than their less hostile counterparts [144]. In another study in which couples engaged in a supportive discussion and a marital problem discussion across two separate sessions, those couples who were more hostile produced more IL-6 after the conflict discussion than the supportive discussion (113 vs. 45%). In contrast, less hostile couples' IL-6 production was similar after both discussions (70 vs. 65%) [88].

Cognitive engagement (the use of cognitive processing words) during a marital disagreement is associated with a dampened inflammatory response. More cognitively engaged individuals produced less IL-6 and TNF-α in the following 24 h after a disagreement compared to less cognitively engaged individuals [145]. In addition, those who were more cognitively engaged had lower

Table 19.1 Summary of key characteristics and health behaviors that influence inflammation

Individual characteristics/health behaviors	Effects on inflammation
Aging	↑ IL-6, TNF-α, CRP [44–47, 49, 50, 53, 54]
Obesity/higher BMI	↑ CRP, IL-6, TNF-α [49–63, 71]
Weight loss	↓ CRP, IL-6, IL-18, TNF-α [64–67, 69]
Sex	CRP: females>males [78–80]
Depression	↑ IL-1, IL-6, CRP [101–105, 108–110]
Anxiety	↑ TNF-α, IL-6, CRP [116–120]
Low social economic status	↑ TNF-α, IL-6, CRP [55, 129–132]
Low social support/poor martial quality	↑ IL-6, CRP [88, 138–140, 142]
Smoking	↑ TNF-α, IL-6, IL-8, CRP [79, 151–167]
Exercise	Immediate: ↑ IL-6, IL-8, IL-15 [168–172] Long term: ↓ CRP, IL-1, IL-6, IFN-γ [174–178, 180, 181] ↑ IL-10 [176, 177]
Poor diet	↑ CRP, IL-1, TNF-α, IL-6 [190–197]
Poor sleep	↑ IL-6, TNF-α, and CRP [211–215] ↓ IL-10 [215]

absolute levels of IL-6 and TNF-α than those who were less cognitively engaged at baseline [145].

Marital stress may be particularly detrimental if combined with other known health risk factors, such as BMI or sagittal abdominal diameter. Women with larger waists showed a stronger positive association between marital stress and CRP than women with smaller waists [146]. Given that having higher levels of CRP raises cardiovascular disease risk [147], the combination of marital stress and having a large waist may be particularly prognostic for heart problems. See Table 19.1 for a summary of characteristics and health behaviors that affect inflammation.

19.7 Health Behaviors and Inflammation

19.7.1 Smoking

Smoking tobacco has been linked to the development of many chronic diseases, such as heart disease, stroke, diabetes, cancer, and chronic airway inflammation such as chronic obstructive pulmonary disease and continues to be the most preventable cause of illness and death in the United States [148]. On average, adults who smoke cigarettes die 14 years earlier than nonsmokers [149]. Smokers' greater inflammatory state may underlie the increased risk of developing chronic diseases and premature death [150].

Smoking appears to elevate CRP [151–153]. In large-scale, population-based studies across several countries, male and female smokers had higher CRP than nonsmokers [79, 154–157]. CRP levels increase with smoking exposure in a dose-dependent manner [158, 159]. Furthermore, CRP remained higher in former smokers even 10–20 years following smoking cessation compared to those who have never smoked [154, 160, 161]. Lifetime smoking exposure elevates CRP levels in both smokers and former smokers [152, 162]; specifically, greater smoking exposure is associated with higher CRP levels in smokers and slower CRP decline after smoking cessation.

Smoking also enhances IL-6 and TNF-α production. Male and female smokers had substantially higher IL-6 compared to former smokers and nonsmokers [155, 163–165]. Similar to the relationship between CRP and smoking exposure, the greater number of cigarettes smoked per day, the higher circulating IL-6 in current smokers [164]. In former smokers, IL-6 remained elevated compared to nonsmokers and decreased significantly as abstinence increased [164]. Male smokers had higher TNF-α than nonsmokers; among smokers, greater tobacco exposure (i.e., pack years) was associated with more TNF-α [166]. An additional study suggested that

smokers may also have higher IL-8 and monocyte chemotactic protein (MCP)-1 than nonsmokers [167].

19.7.2 Exercise

Exercise increases proinflammatory cytokine production [168]. Acute IL-6, IL-8, and IL-15 increases during and following exercise have been consistently demonstrated [169–172]. In the laboratory, endotoxin was administered to young healthy males during rest, following exhaustive exercise, or after an injection of IL-6 [173]. In response to the endotoxin, the exercise and IL-6 groups' plasma TNF-α rise was attenuated compared to the rest group [173]. These results suggest that exercise-induced elevations of IL-6 may have anti-inflammatory effects.

Many studies have shown that increased physical activity lowers inflammation. In population-based studies, more physically active adults had lower serum CRP levels, even when controlling for possible demographic confounds and health behaviors [174, 175]. Among older men, higher fitness levels were associated with lower IL-6 and higher IL-10 [176].

Longitudinal studies also demonstrate the anti-inflammatory benefits of exercise. In a 12-week study, coronary heart disease patients who underwent an intense aerobic training program had lower IL-6, IL-1, and IFN-γ levels and higher levels of the anti-inflammatory cytokine IL-10 compared to their baseline levels [177]. Furthermore, at the end of the study, CRP levels had improved significantly in all participants; among those at the highest risk for developing type 2 diabetes, CRP was 46% lower [177].

CRP levels dropped following a 2-month exercise training program in women [178]. However, women in the moderate weight-reduction quartile showed the most significant CRP decreases, even over those in the largest weight-reduction quartile. These data suggest that women who had the greatest weight loss may have been the result of overtraining, which can lead to increased inflammation [178].

Patients undergoing an exercise and pharmacological (i.e., pravastatin) intervention trial had similar reductions in MCP-1, regardless of exercise assignment [179]. However, the combination group's IL-8 levels decreased significantly more than the drug use only group [179], suggesting that exercise provided additional anti-inflammatory benefits beyond the pharmacological intervention.

Yoga practice also may reduce inflammation. For example, yoga reduced IL-6 and CRP levels in patients with chronic heart failure compared to pre-yoga baseline levels [180]. In a study of healthy participants, expert yoga practitioners had 41% lower serum IL-6 levels compared to novice yoga practitioners [181]. In addition, the novice group was 4.75 times as likely to have detectable CRP levels compared to the expert group. Following an acute stressor, stimulated IL-6 production in the expert group was lower compared to the novice group, suggesting that extended yoga practice may buffer stress-induced proinflammatory cytokine elevations [181].

19.7.3 Nutrition

Large-scale epidemiological studies demonstrate relationships among diet, health, and inflammation. Diets that are high in refined grains, processed meat, sugar, saturated and *trans*-fatty acids, and low in fruits, vegetables, and whole grains promote inflammation and increase the risk for cardiovascular disease and type 2 diabetes [182–185]. Diets are becoming increasingly less healthy, therefore it is important to understand the ways dietary components can elevate inflammation.

The intake of certain macronutrients may produce oxidative stress and lead to inflammation. Oxidative stress results from the metabolism of food and can promote inflammation through activation of the NF-κB pathway [186]. In particular, ingestion of glucose is associated with greater oxidant production and increased NF-κB activity [187, 188]; intravenous administration of glucose raises circulating levels of IL-6 and TNF-α [189, 190]. Moreover, metabolism of high-fat meals begets

increased levels of glucose and triglycerides that can enhance oxidative stress and promote increases in IL-6 and CRP [191]. In contrast, higher fruit and vegetable intake is associated with lower oxidative stress and inflammation, which may counteract the proinflammatory responses to high saturated fatty meals [190, 192].

Some dietary components are the molecular precursors of proinflammatory cytokines. For instance, the omega-6 (*n*−6) polyunsaturated fatty acid (PUFA), arachidonic acid (AA), found in refined vegetable oils, such as corn, sunflower, and safflower, is a major substrate in the synthesis of eicosanoids, molecules that help regulate the intensity and duration of the inflammatory response [193]. Overconsumption of *n*−6 PUFAs increases the production of IL-1, TNF-α, and IL-6 [194, 195]. In contrast, the omega-3 (*n*−3) PUFAs found in fish, fish oil, and flax seed decrease the production of inflammatory eicosanoids and cytokines [193, 195]. Two key *n*−3 PUFAs, eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), can decrease NF-κB activity and TNF-α transcription in response to endotoxin exposure [196, 197].

19.7.4 Sleep

Sleep is essential for good health. Short sleep duration (<7 h/night), poor sleep quality, and extended sleep latency are associated with higher risk for all-cause mortality [198–200]. Sleep disruptions also play a role in inflammatory-related diseases and conditions. For example, disrupted sleep is thought to advance the onset of type 2 diabetes [201] and is a prominent feature of major depressive disorder [202].

The relationship between sleep and proinflammatory cytokines is complex and bidirectional. Circulating levels of IL-6, TNF-α, and IL-1 exhibit a diurnal rhythmicity such that peak levels occur during the early night and reach a nadir in the morning [30, 31]. Cortisol and growth hormone also exhibit a circadian rhythm, suggesting that the effect of sleep on the immune system may be mediated in part through changes in hormones [203]. Thus, cytokine levels are linked to the onset of sleep. Although it is unclear why these variations in cytokine levels occur with the onset of sleep, nonrapid eye movement (NREM) sleep may serve to reallocate energy resources from wakefulness activities to immune responses, which combat latent infections [204].

Consistent with this idea, healthy volunteers injected with endotoxin show increases in the amount and intensity of NREM sleep [205, 206]. Additionally, cytokines themselves produce alterations in normal sleep functions. For example, the administration of IL-1, TNF-α, and IL-6 produces increases in NREM sleep and decreases in rapid-eye movement (REM) sleep for both animals and humans [207, 208]. Taken together, these findings suggest that cytokines are not only influenced by sleep but also actively regulate sleep activities.

Disruptions of sleep and sleep disorders may affect health through elevations of proinflammatory cytokines. As few as 4 h of sleep loss results in greater NF-κB activation and higher morning levels of IL-6 and TNF-α compared to a night of uninterrupted sleep [209, 210]. Similarly, extensive total sleep deprivation (e.g., staying awake for 88 or more consecutive hours) elevates IL-6 and CRP [211, 212].

The immunomodulatory effects of chronic sleep loss are observed in patients with obstructive sleep apnea (OSA). Patients with OSA exhibit higher nighttime levels of plasma TNF-α and IL-6, which increase after each nighttime episode of OSA, and lower levels of the anti-inflammatory marker, IL-10, compared to control patients [213]. This activation of the inflammatory response during sleep may partially account for the elevated levels of CRP and increased risk for cardiovascular disease observed in patients with OSA [214].

19.7.5 Inflammation and Cellular Aging

Burgeoning data suggest that psychological stress accelerates the cellular aging of the immune system [215–219]. A telomere is a group of nucleoprotein complexes that cap chromosomes to protect and stabilize their integrity across the lifespan [220]. Telomere length is a

proxy measure of the biological age of a cell. Shorter telomeres limit the amount of cellular replication, which indicates how close the cell is to death [220, 221]. Young women who were more stressed had shorter telomeres compared to those who were less stressed [215, 219]. Dementia caregiving, a chronic stressor, in older adults was also associated with shorter telomeres and higher TNF-α production [218]. Thus, it appears that stress contributes to accelerated cellular aging.

The evidence-linking stress and telomere shortening suggests that inflammation could be a common biological pathway [222]. In fact, higher levels of inflammation can activate T-cell proliferation, a process that in turn leads to shorter telomeres [223]. Chronic stress also increases oxidative stress [215], which promotes telomere shortening during replication [223]. Because inflammation plays a role in cellular aging, it seems plausible that biological, psychological, and psychosocial factors, as well as health behaviors, may affect telomere length.

Psychological factors like mood disorders and psychosocial factors such as negative childhood experiences are related to shorter telomeres. In a study comparing individuals with mood disorders to healthy, age-matched controls, those with a diagnosed mood disorder had shorter telomeres [216]. Another study showed that patients with major depression had shorter telomeres compared to those without major depression [224]. Childhood maltreatment in young adults has been associated with shorter telomeres [225]. Older adults who experienced an adverse event during childhood had shorter telomeres and higher IL-6 levels than those who did not [226]. These findings suggest that mood disorders as well as negative events from childhood can have lasting effects on cellular aging.

Biological factors and some health behaviors can also modify telomere length. Aging has been associated with shorter telomeres [219, 227] Age-related telomere shortening has been linked to age-related diseases and mortality [228]. Obese women and smokers also have shorter telomeres [219, 227]. Less physically active participants had shorter telomeres than more physically active ones [229]. Therefore, factors that are known to increase inflammation also shorten telomere length. These data support the conclusion that inflammation may be a biological pathway linking stress and cellular aging.

19.8 Conclusion

Understanding inflammation requires knowledge of multiple biological, psychological, and psychosocial factors, as well as health behaviors. Higher proinflammatory cytokines are associated with aging, obesity, depression, anxiety, poor quality relationships, smoking, poor diet, exercise, and sleep habits. These factors independently impact inflammation but they can also coincide to have additive effects on inflammation.

Socioeconomic status provides an excellent example of how several factors converge to affect inflammation. Individuals with low SES are more likely to smoke, abuse alcohol, be sedentary, have poorer diets, sleep less, and experience more stress and depression [127]. The relationship between low SES and poor health still exists despite statistically controlling for these negative factors, suggesting that the sum effect is greater than its parts.

Health behaviors may buffer these negative psychosocial factors and ameliorate harmful effects on inflammation. Increasing physical activity lowers proinflammatory mediators [177–179]. Restorative yoga participation lessened inflammation in chronic heart failure patients [180]. Weight loss without increasing physical activity also lowered inflammation [67, 68, 71]. Smoking cessation appears to reduce elevated cytokines relatively quickly; however, CRP levels in former smokers may take 10–20 years to drop to those of nonsmokers' [154, 160, 161]. In addition, diets high in fiber and low in saturated fats are also associated with lower inflammation [190, 192].

Because inflammation contributes to many chronic diseases such as cardiovascular disease and diabetes, controlling or reducing inflammation is important. Clearly individual characteristics including age and sex cannot be modified; however, helping individuals change their poor

behavioral habits and reducing inflammation may both extend longevity and increase the quality of life.

Taken together, inflammation is a transactional process; many factors can overlap and have additive effects. The observation that proinflammatory cytokines accelerate immune cell replication and cellular aging is a recent finding, suggesting a new and exciting direction for further PNI-focused research. Thus health research using a PNI lens will continue to pioneer novel and integrative investigations into the factors that influence the relationship between inflammation and disease.

Important information researchers should consider when studying inflammation:
• Inflammation is the result of interactions among many biological pathways including the autonomic nervous system, hypothalamic–pituitary–adrenal axis, and the innate immune system
• Psychological stress induces proinflammatory cytokine release
• Psychosocial factors and health behaviors impact chronic inflammation through direct and indirect pathways
• Age is positively associated with inflammation
• Inflammation is important for physical and psychological health; the pathway between the brain and the immune system is bidirectional

Important information clinicians should consider:
• Inflammation is the result of interactions among many biological pathways including the autonomic nervous system, hypothalamic–pituitary–adrenal axis, and the innate immune system
• Controlling/reducing chronic inflammation is important for good physical and psychological health
• Although clinicians cannot change a patient's sex, age, or SES, creating an action plan based on the patient's needs could include
– Weight reduction
– Increasing exercise
– Making better nutritional choices
– Increasing hours slept at night
– Providing mental health referrals

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