

## Oxford Research Encyclopedia of Psychology

### **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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### **Summary and Keywords**

Inflammatory markers provide invaluable tools for studying health and disease across the lifespan. Inflammation is central to the immune system's response to infection and wounding; it also can increase in response to psychosocial stress. In addition, depression and physical symptoms such as pain and poor sleep can promote inflammation and, because these factors fuel each other, all contribute synergistically to rising inflammation. With increasing age, persistent exposure to pathogens and stress can induce a chronic proinflammatory state, a process known as *inflamm-aging*.

Inflammation's relevance spans the life course, from childhood to adulthood to death. Infection-related inflammation and stress in childhood, and even maternal stress during pregnancy, may presage heightened inflammation and poor health in adulthood. In turn, chronically heightened inflammation in adulthood can foreshadow frailty, functional decline, and the onset of inflammatory diseases in older age.

The most commonly measured inflammatory markers include C-reactive protein (CRP) and proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ). These biomarkers are typically measured in serum or plasma through blood draw, which capture current circulating levels of inflammation. Dried blood spots offer a newer, sometimes less expensive collection method but can capture only a limited subset of markers. Due to its notable confounds, salivary sampling cannot be recommended.

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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Inflammatory markers can be added to a wide range of lifespan developmental designs. Incorporating even a single inflammatory assessment to an existing longitudinal study can allow researchers to examine how developmental profiles and inflammatory status are linked, but repeated assessments must be used to draw conclusions about the associations' temporal order and developmental changes. Although the various inflammatory indices can fluctuate from day to day, ecological momentary assessment and longitudinal burst studies have not yet incorporated daily inflammation measurement; this represents a promising avenue for future research.

In conclusion, mounting evidence suggests that inflammation affects health and disease across the lifespan and can help to capture how stress “gets under the skin.” Incorporating inflammatory biomarkers into developmental studies stands to enhance our understanding of both inflammation and lifespan development.

Keywords: inflammation, inflamm-aging, lifespan development, biomarker, methodology

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## **Lifespan Developmental Science and the Importance of Inflammation**

Lifespan developmental psychology seeks to describe, explain, and find ways to optimize individuals' developmental paths from birth to death. According to a lifespan developmental perspective (Magnusson & Cairns, 1996), the whole person consists of multiple interacting subsystems—genes, cells, tissues, and organs, as well as thoughts, feelings, and memories. In turn, individuals are nested within larger systems of families, communities, and cultures. An individual's development is the result of these nested factors over time.

Inflammation serves as an important part of the body's defense against pathogens and tissue damage. Like some other organ systems, the innate immune system and its inflammatory response develop to maturity after infancy and decline in older adulthood (Simon, Hollander, & McMichael, 2015). Chronically elevated inflammation sets the stage for developing a host of age-related diseases, from cardiovascular disease to diabetes to Alzheimer's disease (Franceschi & Campisi, 2014). Thus, inflammation shapes an individual's broader health trajectory and contributes to his or her health span (i.e., the number of healthy years to be lived).

Immune system aging, inflammation, and their chronic-illness consequences do not emerge in a deterministic way, resistant to outside influence and identical for everyone. Rather, these processes are shaped by challenge or stress at other levels of the system—whether the threat is viral, bacterial, or psychological. Research in the past 10 years has revealed that, in turn, inflammation can affect emotion, sociability, motivation, and cognitive function (Miller, Maletic, & Raison, 2009). Thus, individuals' unique

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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constellations of characteristics, stressors, and inflammatory burden lead to widely varying paths through adulthood and old age. Collecting inflammatory biomarkers in lifespan developmental research can enhance our understanding of psychosocial and cognitive development, in addition to health and longevity. This article begins by describing the biological pathways of inflammation. It then reviews major research findings with regard to stress, inflammation, and development. Finally, it describes the practical details of measuring inflammation and considerations for incorporating inflammatory biomarkers into developmental designs.

## **What Is Inflammation? Necessary Functions and Unintended Consequences**

### **Inflammation in Response to Tissue Damage and Infection**

When tissue is damaged and pathogens invade, macrophages, a type of immune cell, swallow up the invaders at the injured site and clean up debris (Medzhitov, 2008). Blood vessels dilate to allow other macrophages and monocytes to enter from the bloodstream; these defenders continue to destroy the pathogens and begin to repair affected tissue. At the same time, macrophages produce and release *proinflammatory cytokines*, which then dispatch other cells throughout the body for a continued inflammatory response. Two proinflammatory cytokines are most commonly studied: interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ). IL-6 triggers a third common inflammatory marker, C-reactive protein (CRP), which is synthesized in the liver. As the inflammatory response is underway, anti-inflammatory cytokines, such as interleukin-10 (IL-10), are also triggered to inhibit further signaling and terminate the inflammatory response. (Medzhitov, 2008)

Immunologists believed 30 years ago that an immune response in the body could not reach the brain, but more recent research has shown that brain cells *do* detect peripheral inflammation and continue the inflammatory cascade by releasing proinflammatory cytokines in brain tissue (Miller et al., 2009). This neural inflammation accounts for the classic behavioral and psychological symptoms of inflammation, called *sickness behaviors*—namely, lethargy, depressed mood, social withdrawal, anhedonia, and cognitive problems (Miller et al., 2009).

### **Inflammation in Response to Psychological Stress**

Psychological stress also can provoke inflammatory responses, even in the absence of tissue damage and infection. Specifically, feeling stressed—by appraising a situation as more than one can handle—activates two fight-or-flight circuits in the brain: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary axis

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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(Slavich & Irwin, 2014). The sympathetic signal travels quickly through the sympathetic nervous system and, by releasing norepinephrine, triggers production and release of proinflammatory cytokines through the nuclear factor  $\kappa$ B (NF- $\kappa$ B) pathway (Bierhaus et al., 2003). The comparatively slower HPA axis releases hormones from the pituitary and adrenal glands that in turn release cortisol (Slavich & Irwin, 2014). Among its many functions, cortisol can inhibit the activity of proinflammatory cytokines and upregulate anti-inflammatory cytokines. Inflammation also can increase cortisol output, which in turn serves to dampen the inflammatory response (Silverman & Sternberg, 2012).

## **Inflammation and the Parasympathetic Nervous System**

Activation of the parasympathetic nervous system can temper the acute inflammatory response (Cooper et al., 2015). Indeed, the vagus nerve inhibits the NF- $\kappa$ B pathway to inflammation, thus reducing the production of proinflammatory cytokines (Tracey, 2009). In other words, the vagus nerve serves as a set of brakes on inflammatory responses. With greater vagal activation (i.e., more parasympathetic nervous system activation, or “resting and digesting”), the brakes are pressed more firmly and less inflammation results. When the brakes are removed (i.e., less parasympathetic activation), inflammation can increase. Experimental evidence is convincing: directly stimulating the vagus nerve decreases inflammatory responses and may even effectively treat some inflammatory diseases (Liezmann, Stock, & Peters, 2012; Pavlov & Tracey, 2005).

## **Inflammation Over Time: Wear and Tear**

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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Inflammation typically increases with a lifetime of exposure to stressors of all types—bacterial, viral, or psychological—resulting in a *proinflammatory phenotype* characteristic of older age (Franceschi et al., 2000). In turn, this heightened inflammation can predispose people to many age-related diseases, including cardiovascular disease, atherosclerosis, Alzheimer’s disease, osteoporosis, and diabetes (Franceschi & Campisi, 2014). This process is referred to as *inflamm-aging* (Franceschi et al., 2000).

The inflamm-aging proinflammatory phenotype can emerge through many systemic biological changes. For example, as chronic stressors and continued pathogen exposure promote more chronic inflammation, leukocytes can begin to resist cortisol’s dampening effects, resulting in glucocorticoid insensitivity (Cohen et al., 2012; Stark et al., 2001). Likewise, consistently high levels of cortisol (such as those generated in the early stages of a chronic stressor) can desensitize leukocytes to cortisol’s effects (Rohleder, 2014). In turn, cortisol’s ability to counteract inflammation declines.

Moreover, inflammation speeds cell turnover, aging the immune system and leading to the accumulation of senescent cells (Freund, Orjalo, Desprez, & Campisi, 2010). Aged cells secrete proinflammatory cytokines, feeding the vicious cycle of inflamm-aging (Franceschi & Campisi, 2014). Destructive inflammatory processes can occur in the body and brain alike: in the brain, TNF- $\alpha$  can kill neurons directly, and the broader inflammatory cascade can demyelinate neurons and degrade brain plasticity (Miller et al., 2009). Once a person acquires a vulnerable proinflammatory phenotype, any number of inflammation-based diseases may emerge (Franceschi et al., 2000). One’s genetic profile may play a role in determining which conditions develop (Franceschi et al., 2000).

### **System-Specific Dysregulation: Chronic Inflammation and Atherosclerosis**

Chronic inflammation spurs atherogenesis, the process of developing plaque in the arteries, which results in atherosclerosis. Through this route, inflammation also contributes to heightened risk for coronary heart disease, stroke, and Type 2 diabetes, among others (Chin et al., 2013; Lundervik et al., 2014; Stein & Johnson, 2010).

Atherosclerosis develops via both heightened low-density lipoproteins (LDLs, so-called bad cholesterol) and inflammation. Fatty streaks develop in the lining of the blood vessels. These areas become inflamed and thus attract leukocytes to repair them (Libby, Ridker, & Hansson, 2011). Over time, these repair attempts continually trap more LDLs in the repair site, and atherosclerotic plaque forms on the blood vessel, restricting blood flow. When ruptured, the plaque can release a blood clot, which can travel through the bloodstream and block blood flow to the brain or heart, resulting in stroke or heart attack.

### **System-Specific Dysregulation: Chronic Inflammation and Cancer**

Chronic inflammation plays a role in the creation, development, and spread of cancer (Balkwill, Charles, & Mantovani, 2005). In part, proinflammatory cytokines and the NF- $\kappa$ B pathway block the protective effects of tumor suppressor genes, such as *p53*, and prevent

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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the early destruction of cells with cancer potential (Balkwill et al., 2005; Hussain, Hofseth, & Harris, 2003). Proinflammatory cytokines secreted within the tumor microenvironment promote blood vessel creation, providing the tumor with access to the fuel necessary for growth (Hussain et al., 2003). Essentially, the tumor “hijacks” the natural wound healing process to aid in its own protection and development. In addition, a chronic proinflammatory signal can recruit tumor-associated macrophages directly, helping the tumor to metastasize, that is, invade other tissues and therefore spread throughout the body (Wu & Zhou, 2009). Thus, chronic inflammation creates the environment for malignant tumors to grow and thrive.

## **Inflamm-Aging and Lifespan Theories: Shared Evolutionary Roots**

An evolutionary perspective grounds theories of both lifespan development and inflamm-aging. According to the lifespan perspective (Baltes, Lindenberger, & Staudinger, 2006), the genes that evolution has selected target survival through reproduction and reproductive success. Therefore, protective alleles act earlier in the lifespan and lose their ability to safeguard health as age increases (Whitbourne, 2002). This incomplete biological architecture (Baltes et al., 2006) creates an increased demand for outside resources and support from the environment as people age. Continued biological decline also means that these resources become less effective with age, creating the need for even more environmental support. In this way, the dynamics of biology and environment creates widely varying paths through adulthood.

Some biologists argue that the disease risks associated with inflamm-aging are a direct result of natural selection—that a robust immune response in childhood dooms adults to wear and tear in later life (Licastro et al., 2005). According to this “pay later” theory, the people who survive the risky stage of childhood—a time when the immune system’s memory for dangerous pathogens is still naive or limited—likely have genetic profiles that equip them with robust inflammatory responses to threats. Because the system also responds to psychosocial stress, the inflammatory load of a robust responder would be greater throughout adulthood into old age than that of a low responder. The inflammatory response of the strong responders also may be more likely to silence the inhibitory systems that act as a brake on inflammation—for example, cortisol, via glucocorticoid receptor insensitivity (Stark et al., 2001). People who have less extreme genetic variants, and thus weaker inflammatory responses, are less likely to survive through infancy and early childhood. The compatibility of inflamm-aging and lifespan developmental thinking reflects the potential for incorporating inflammatory biomarkers into developmental research.

## **Inflammation, Stress, and Depression—in Many Forms**

Stress is often distinguished in terms of its time course: whether the stressful event and its effects are time-limited or chronic. Time-limited stressors are treated as one-time events, where inflammation is measured before and after a difficult task. For example, inflammation reliably increases after the Trier Social Stress Test, a high-pressure, socially evaluative public speech and timed arithmetic task, and similar challenges (Kirschbaum, Pirke, & Hellhammer, 1993; Marsland, Walsh, Lockwood, & John-Henderson, 2017). Hostile marital disagreements also elicit inflammatory increases in couples (Kiecolt-Glaser et al., 2005).

Classic examples of chronic stress include dementia family caregiving and socioeconomic disadvantage; both relate to increased inflammation (Chen, McLean, & Miller, 2015; Kiecolt-Glaser et al., 2003). For example, in a six-year longitudinal study, both current and bereaved spousal dementia caregivers' IL-6 increased at four times the rate of the control participants' inflammation (Kiecolt-Glaser et al., 2003). In two national adult samples, more socially isolated people had higher CRP in subsequent years than the socially integrated, adjusting for baseline CRP (Yang et al., 2016). Both low socioeconomic status (SES) and black race are associated with higher inflammation (Chen et al., 2015; Stepanikova, Bateman, & Oates, 2017). Above and beyond the effects of race and SES, people who have experienced more frequent discrimination on the basis of race or SES have higher inflammatory markers than people who have escaped discrimination (Stepanikova et al., 2017).

### **The Exacerbating Role of Depression**

Depression, whether mild or syndromal, can fuel inflammation. For example, people who had more frequent depressive episodes across five years had higher CRP at the end of that period than those with fewer episodes (Copeland, Shanahan, Worthman, Angold, & Costello, 2012). Higher numbers of depressive symptoms can act in tandem with an immune or behavioral challenge to provoke larger inflammatory responses. For instance, both older adults and pregnant women with elevated depressive symptoms had more pronounced and prolonged cytokine increases to flu vaccine than those with fewer depressive symptoms (Christian, Franco, Iams, Sheridan, & Glaser, 2010; Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003). Similarly, higher levels of depressive symptoms were associated with a greater inflammatory response to stressful lab tasks (Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013; Pace et al., 2006). Moreover, inflammatory responsiveness may fail to habituate with repeated stressors (McInnis et al., 2014).

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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In turn, inflammation primes depression. During an inflammatory response, monocytes traffic from the periphery to the brain, where cytokine signaling induces sickness behaviors that closely resemble the cardinal symptoms of depression: negative mood, lethargy, cognitive problems, heightened pain sensitivity, and social withdrawal (Miller et al., 2009). Further, people with both treatment-resistant depression and elevated inflammation had fewer depressive symptoms following treatment with a TNF- $\alpha$  antagonist (Raison et al., 2013). That is, when depression coincided with elevated inflammation, reducing that inflammation led to a reduction in depressive symptoms. Conversely, cytokine-based therapies that increase inflammation can induce depression in almost half of treated patients (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Udina et al., 2012). Thus, the bidirectional paths between inflammation and depression likely expedite the journey down the road to inflamm-aging.

Depression, stress, and inflammation form a risky triumvirate. People with a history of depression experience more major life stressors and minor hassles than people with no such history (O'Grady, Tennen, & Armeli, 2010). Thus, depression may increase the frequency of stress-triggered inflammatory responses. Likewise, stressful life events can spark depressive episodes: In a case-control comparison, people who had recently developed major depressive disorder (MDD) were more than two times as likely to have experienced a major life stressor in the prior six months as were people without MDD (Monroe, Slavich, & Georgiades, 2009).

Depression's links to obesity further raise the stakes for inflammation. Depression is associated with a greater-than-50% risk of becoming obese; the risks for obese people to develop depression are equally high (Luppino et al., 2010). In turn, people with more abdominal fat show larger cytokine responses to lab stressors (McInnis et al., 2014).

In short, researchers have found that, regardless of the measurement approach and time scale, heightened inflammation can accompany psychosocial stress and depression. Because the way that people handle stress changes normatively across the lifespan (Charles, 2010), and because inflammation increases with age (Franceschi et al., 2000), it is also valuable to consider the role of developmental change in the links between stress and inflammation.

## **Inflammation, Stress, and Development: Empirical Findings Across the Lifespan**

Studies of people at all ages have demonstrated the value of examining inflammation and development across the lifespan: stress, inflammation, and other health factors seem to track together over time. Inflammation is a lifelong, health-relevant biomarker; it can be measured from toddlerhood to death. Also, early-life infection and psychosocial stress

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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may cast long shadows over inflammatory load and disease risk in adulthood and later life.

### **Inflammation's Relevance From Childhood to Old Age**

Although most research has focused on the health importance of chronic inflammation in middle age and older adulthood, inflammation is also a meaningful health marker in early life. In a study of young people ages 7–18, obese youths had higher CRP than their normal-weight counterparts; they also produced less IL-10, an anti-inflammatory cytokine that keeps inflammation levels in check (Mattos et al., 2016). These children face greater risks for developing pain and Type 2 diabetes in childhood, both of which can be fueled by inflammation, and they are likely to experience magnified health problems in adulthood (Smith, Sumar, & Dixon, 2014). In asthma, a condition more common in childhood than adulthood, inflammation constricts the airways (Martinez, 2001). Among asthmatic children with high family stress, short-term stressors provoked increases in asthma-related inflammatory markers; the effect of acute stress on asthma-related inflammation was not present among children in lower-stress families (Marin, Chen, Munch, & Miller, 2009). Thus, both general and condition-specific inflammation in childhood can insult health and degrade quality of life, in youth and older age alike.

Heightened inflammation also predicts poorer health and physical function in young adults. Participants of the Dunedin longitudinal cohort study in New Zealand, born in the same year and largely disease-free as of age 38, were studied at 26, 32, and 38 years old (Belsky et al., 2015). Each person's biological age was calculated from his or her CRP, along with 17 other health indicators. The 38-year-olds with older biological age scores had weaker grip strength, poorer balance and short-term memory, and slower processing speed, and appeared older to observers than same-age peers with healthier biological profiles. The biologically older participants had also shown steeper declines in these areas across the 12 years of the study.

Only at the extreme end of the lifespan does inflammation's predictive value degrade: healthy centenarians have high inflammation, similar to that of aged people in poor health (Salvioli et al., 2009). However, centenarians have high anti-inflammatory cytokine activity, suggesting the importance of examining anti-inflammatory cytokines alongside proinflammatory activity, particularly in old age.

### **Early Infection and Stress Can Predict Later Inflammation**

Many developmental studies of inflammation have found that early-life infection or psychosocial stress portend greater inflammatory burden and disease risk in adulthood and later life (e.g., Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016). These studies have focused on developmental continuity—the notion that risks tend to accumulate and snowball over time, fueling a vicious cycle. To illustrate, families with lower SES tend to

## Inflammation As a Biomarker Method in Lifespan Developmental Methodology

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have more limited access to healthcare, poorer living conditions, and unhealthier diets, which can increase children's risk for infection and illness; in turn, being sicker in early life may limit normal growth, daily function, opportunities, and eventually employability, which can reinforce barriers to healthcare resources. Indeed, people who survived more infections in childhood have poorer health as adults than those who experienced fewer childhood illnesses (Blackwell, Hayward, & Crimmins, 2001). Early-life psychosocial adversity also may predict higher inflammation in adulthood: An 18-study meta-analysis of more than 16,000 participants found that people who had been abused or neglected in childhood had higher CRP, IL-6, and TNF- $\alpha$  levels as adults (Baumeister et al., 2016).

Studies of stress and inflammation in children and adolescents have strengthened this line of research by avoiding retrospective reporting bias and identifying proximal outcomes that explain the long-reaching effects of childhood adversity. Indeed, prospective studies show that adversity even prior to birth, in the form of maternal stress during pregnancy, may predispose individuals to develop higher inflammation over time. For example, maternal adversity during pregnancy was prospectively associated with greater CRP in their middle-aged offspring 40 years later (Slopen et al., 2015). Similarly, prenatal maternal depression prospectively predicted greater offspring CRP 25 years later (Plant, Pawlby, Sharp, Zunszain, & Pariante, 2016).

In the National Health and Nutrition Examination Survey (NHANES), youth ages 3–16 with lower family income also had higher CRP; obesity, illness, and smoke exposure accounted for this difference (Dowd, Zajacova, & Aiello, 2010). This finding was replicated in adolescents: in addition to the links between low SES and higher inflammation, adolescents from low-SES families had greater glucocorticoid resistance (Chen et al., 2015). Further, low-SES teenagers evidenced even higher inflammation when they *shifted and persisted* less (i.e., were less able to find meaning and positively reframe stressors).

In a prospective longitudinal study, children who had experienced greater adversity (abuse, neglect, or parental separation) from birth to age 8 had higher CRP when they were 10 and 15 years old; they also showed greater increases in CRP over that period (Slopen, Kubzansky, McLaughlin, & Koenen, 2013). These links were explained by greater body mass index (BMI) and recent depression. Another prospective longitudinal study assessed ties between bullying in childhood and inflammation in young adulthood (Copeland et al., 2014). On average, CRP increased from childhood to adulthood, and people who were bullied in childhood had steeper increases than people who were not. Further, there was a dose-response relationship between years of being bullied and CRP levels.

On the other hand, youth who bullied others had smaller increases into young adulthood compared to bullying victims, as well as those uninvolved with bullying—a pattern that the authors attributed to higher social status. Using prospective longitudinal designs and varied methods (self-report, other-report, and direct observation), studies of child and adolescent populations have corroborated findings from retrospective studies of adults.

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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Examining early life prospectively also has revealed that potent stressors extend beyond abuse and neglect, that effects of stress appear as early as in childhood, and that they may operate partially through depressive symptoms and obesity in childhood.

## **Inflammation and Stress in Adulthood May Foreshadow Death and Disease in Older Age**

Stress in adulthood can speed age-related increases in inflammation, exacerbating an already dysregulated inflammatory response to threat. In one classic example, the IL-6 levels of chronically stressed dementia family caregivers increased at four times the rate of noncaregiving controls' inflammation (Kiecolt-Glaser et al., 2003). In turn, higher inflammation in adulthood can increase the risk for death and disease in older age. In members of the Framingham Heart Study, greater inflammatory burden—a composite calculated from nine inflammatory indices—in middle age predicted heightened risk for cardiovascular disease and mortality approximately 30 years later, after accounting for blood pressure, cholesterol, glucose, kidney function, and epigenetic age (Murabito et al., 2017). In samples of middle-aged adults (45–59 years old), greater inflammatory reactivity to stress predicted higher blood pressure (Brydon & Steptoe, 2005) and carotid artery stiffness (Ellins et al., 2008) over time—two notable precursors to cardiovascular disease.

## **Historical Shifts in Inflammation Across the Lifespan**

The lifespan developmental framework emphasizes the importance of historical context: the time in history when people are born determines their possible paths through life. Generations born before vaccinations succumbed to untreatable viral and bacterial infections at high rates in early childhood. For example, sociologists gathered death records from people in Sweden beginning in 1751, France from 1806, England from 1841, and Switzerland from 1876, up to 1899 (Crimmins & Finch, 2006). Cohorts who enjoyed low death rates in childhood also had lower mortality rates in older adulthood, suggesting that there is a connection between early infection and later-life health, and that both shift with their history-graded context. This hypothesis was supported by a study comparing CRP in Americans to that of the Tsimane people, a preindustrialized society in the Amazon (Gurven, Kaplan, Winking, Finch, & Crimmins, 2008). Whereas U.S. life expectancy is close to 80 years old, Tsimane people expect to live to age 40, similar to Western Europeans' life expectancy in the early 1800s. The prevalence of high CRP was more than three times greater in Tsimane children ages 3–9 compared to U.S. children, likely due in part to infectious disease exposure. Likewise, by early adulthood, Tsimane had spent more years with elevated CRP than had Americans in middle adulthood.

## **Beyond Stress: Symptoms That Fuel Inflammation**

In addition to psychosocial stress and infection, symptoms such as sleep problems and pain synergistically fuel inflammation and are particularly apt to trigger a downward spiral as people enter old age. Sleep dysfunction and pain each independently promote inflammation. People with clinical insomnia had higher plasma levels of IL-6 and CRP five years after the initial assessment (Cho, Seeman, Kiefe, Lauderdale, & Irwin, 2015). Short-term sleep loss does not appear to increase baseline inflammation (Irwin, Olmstead, & Carroll, 2016), but a study of married couples found that partners who slept less in prior nights showed greater inflammatory responses to marital disagreement compared to their well-rested counterparts (Wilson et al., 2017). Thus, short-term sleep loss may induce heightened sensitivity to stressors.

Painful stimuli can elicit inflammatory responses. For example, IL-6 levels increased when healthy participants immersed an arm in an ice bath for as long as they could endure, up to 5 minutes (Griffis et al., 2013). This pattern extends to chronic pain, as those with active knee osteoarthritis exhibited higher IL-6 levels than those without the diagnosis (Quartana, Finan, Page, & Smith, 2015).

Pain and sleep problems mutually exacerbate each other and, together, escalate with age (Smith & Haythornthwaite, 2004). Given its aversiveness, pain heightens arousal, therefore disturbing sleep. In turn, disrupted sleep intensifies pain sensitivity. Rheumatoid arthritis patients who were experimentally sleep-deprived reported greater pain and joint involvement compared to baseline levels (Irwin et al., 2012). These reciprocal influences may exacerbate inflammation synergistically, as suggested by a study of insomnia-diagnosed patients who showed higher pain-evoked IL-6 increases than those without an insomnia diagnosis (Quartana et al., 2015). Stress and depression also disturb sleep and increase pain sensitivity, heightening inflammation (Crettaz et al., 2013; Miller et al., 2009).

## **Measuring Inflammation: General Considerations**

### **Plasma and Serum Samples**

Inflammatory markers can be collected and measured in multiple ways. Currently, blood drawn through a vein is the gold standard for assessing circulating cytokine levels. This approach relies on trained staff and specialized equipment for collection and storage.

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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Cytokine levels in plasma or serum indicate current levels of inflammation in peripheral circulation; stimulation of leukocytes through the use of lipopolysaccharide (LPS) provides another common measure of inflammation. Briefly, peripheral blood mononuclear cells (PBMCs) are treated with LPS, which initiates the release of proinflammatory cytokines to destroy the bacteria (De Groote et al., 1992). Unlike circulating inflammatory markers, which show current levels, stimulated cytokines demonstrate the inflammatory response that would occur when leukocytes encounter a pathogen.

### **Blood Spots**

Blood spots are a newer method for measuring some inflammatory markers; in this procedure, blood from a finger stick is dropped onto filter paper and allowed to dry. Dried blood spots offer multiple advantages in terms of collection and storage. For example, the essential dried blood spot materials, filter papers and lancets, can be taken into the field easily and may be less threatening and painful to participants than those used for blood draws (Meesters & Hooff, 2013). The technique and equipment for blood spot collection are important but require less training than blood draws. In addition, while immediate refrigeration or freezing is preferred, blood captured on filter paper can be stored at room temperature for a week or more without considerable changes in the inflammatory biomarkers themselves (Miller & McDade, 2012). Finally, the processing of dried blood spots is often considerably less expensive than other methods (Meesters & Hooff, 2013). However, dried blood spots offer almost no flexibility for measuring inflammation beyond IL-6 and CRP (McDade, Burhop, & Dohnal, 2004; Miller & McDade, 2012). Thus, dried blood spots may be an effective form of measurement for IL-6 and CRP for large, populationwide studies, or for reaching populations that are unable to travel to the laboratory, but they are not appropriate for measuring most aspects of immune function.

### **Saliva**

Salivary collection of inflammatory biomarkers is also of great interest due to its relative ease of collection compared to blood draws (Slavish, Graham-Engeland, Smyth, & Engeland, 2015). However, salivary cytokine data appear to capture local inflammation better than systemic inflammation (Schapher, Wendler, & Gröschl, 2011). Indeed, salivary assays are subject to confounding by oral disease and bacteria, which are highly prevalent in adults (Yoon, Cheng, Philipone, Turner, & Lamster, 2012). Thus, salivary assessment is not likely to be useful for measuring systemic inflammation (Schapher et al., 2011).

### **Interpreting Inflammatory Data**

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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Inflammation can be affected by many different factors, and thus researchers should consider other factors during measurement and interpretation—that is, by removing out-of-range data, using other predictors as covariates, or screening out participants based on health conditions, medications, or both. For example, having circulating CRP levels above 3 mg/L is considered a meaningful clinical predictor of developing cardiovascular disease; no standardized cutoff exists for IL-6 or TNF- $\alpha$  (Kiecolt-Glaser, Derry, & Fagundes, 2015; Pearson et al., 2003). However, CRP values greater than 10 are commonly excluded from analysis because they may be driven by acute illness rather than chronic, low-grade inflammation (McDade, Hawkey, & Cacioppo, 2006). Smoking and BMI also have pronounced proinflammatory effects (Bennett et al., 2013; McInnis et al., 2014). Race, sex, and age are also standard covariates, because of basic demographic differences (McDade et al., 2006).

Broadly, any illness or medication that alters inflammation should be considered in the recruitment, analysis, and interpretation of data; researchers must weigh the relative magnitude of the confound against its prevalence in the population and balance scientific rigor with generalizability. If the primary objective is to capture inflammatory responsiveness, it is important to exclude users of strong anti-inflammatories such as methotrexate or statins. For researchers interested in generalizability, erring on the side of inclusiveness may be important, particularly in studying older adults and the oldest old. As extreme examples, Swedish national studies of immune function in 80-year-olds and 90-year-olds did not exclude participants based on any health-related criteria, so as to fully describe the factors that affected immune function in both well and ill older people (Wikby, Johansson, & Ferguson, 2002). Importantly, researchers must be cautious and thorough in ruling out alternative explanations for effects on inflammation and inflamm-aging.

## **Incorporating Inflammation Into Developmental Designs**

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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Using inflammatory biomarkers in developmental research will enhance our understanding of paths to health and disease and, given their action in the brain, also may illuminate behavioral and emotional processes across the lifespan that cannot be captured with self-report. Although most developmental studies have examined inflammation in adulthood and older age, inflammation is at work across the entire lifespan, and inflammatory biomarkers can be collected as early as toddlerhood. As a stable clinical indicator, CRP is the most common inflammatory biomarker used in developmental research, particularly in large-scale studies. For proinflammatory cytokines with diurnal variation such as IL-6, the timing of collection should be monitored; systemic IL-6 has a diurnal rhythm, such that it has a low point in the morning and rises over the course of the day—that is, the opposite pattern of the well-established cortisol diurnal rhythm (Nilssonne, Lekander, Åkerstedt, Axelsson, & Ingre, 2016). Inflammatory biomarkers add considerable expense to a research budget: personnel to conduct home or clinic visits, blood-draw supplies (some of which are perishable, such as vacutainer tubes and assay kits), lab space, refrigerated storage, and personnel to process the blood. To control expenses, large-scale national studies often have selected a representative subsample for biomarker assessment. Blood spot collection is most suitable for ambulatory studies of CRP and IL-6 in remote locations; therefore, it may be most easily scaled up in large studies.

### Assessing Inflammation at One Time Point

The added scientific value of one inflammatory biomarker assessment compared to having no biomarker data is tremendous. This type of design can reveal how present inflammation is associated with concurrent health status, age differences, and patterns of behavior and experiences leading up to that point. Adding inflammatory biomarkers to existing large-scale national studies is becoming increasingly common; many such studies gather adults' retrospective reports of childhood experiences to construct a pseudolongitudinal portrait of people's lives. The most striking findings from this type of design have documented connections between childhood maltreatment and inflammation 30 years later (Baumeister et al., 2016).

Although the single-time-point design is indispensable in lifespan research, its limitations are also important to consider. Retrospective reports of early experience may be biased upward or downward, depending on the specific measure. Among adults, maltreatment in childhood is severely underreported (Gilbert et al., 2009), which is likely to mask the magnitude of differences between maltreated people and controls. Alternatively, because evaluations of past events are influenced by one's current state and mood (Schwarz, 1999), other measures of childhood stress may be magnified artificially by present stressors and negative affect.

Further, strong directional conclusions cannot be drawn without adequately considering covariates that occur early in the process. For example, most studies linking child maltreatment to adult inflammation have controlled for adult confounds, but not necessarily for childhood factors such as SES in childhood, childhood BMI, and illnesses experienced in childhood. Likewise, studies examining the unique effects of adults' psychosocial risks and resources on their later inflammation should control for premorbid health conditions and inflammation levels.

Also, such studies can draw conclusions about age *differences*, but not changes across the lifespan. Because sociocultural influences and exposure to pathogens both change with historical shifts, people from different cohorts are not necessarily interchangeable. Furthermore, selection effects create systematically missing data that must be addressed: the sickest people who would have the highest inflammation may not be represented in the sample due to death or disablement.

### Longitudinal Assessment

Panel longitudinal studies are best suited for capturing development with a broad view, and thus are most informative for explaining intraindividual change across life stages. A prospective longitudinal design that assesses both behavior and inflammation at multiple time points offers the greatest naturalistic opportunity for determining temporal order.

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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Such a design is positioned to examine, for example, whether work stress at age 40 uniquely predicts higher inflammation at age 55, above and beyond the role of inflammation levels and other risk factors assessed at age 40.

The pace of the outcome of interest and the typical age of onset should drive the frequency of assessment in a longitudinal panel design. In large, multipurpose studies, intervals range from 2 years (e.g., in the Health and Retirement Study) to 10 years (e.g., in the Midlife in the U.S. study, MIDUS). A longer interval between assessments may be more appropriate for longitudinal studies that begin earlier in adulthood and that aim to predict disease and mortality risks, because many chronic illnesses do not emerge until middle and older age. The transition from a healthy state to disease, frailty, and decline may occur more quickly among older people, and the pace of measurement should follow. Some studies may aim to examine the development of a certain disease process, such as the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study, designed to track the onset of cardiovascular disease; if a study purposefully samples people at high risk for developing the disease, more frequent measurement is appropriate. In short, timing of assessment should track with the expected rate of change.

In addition to examining inflammation at a given point, longitudinal studies can quantify the rate at which chronic inflammation increases, as well as how that rate predicts poorer health. For example, one group of researchers created a pace of aging score, which included changes in inflammation from ages 26–38 (among other biomarker changes) (Belsky et al., 2015). This score was only moderately associated with participants' levels of inflammation and other biomarkers; a faster pace of aging predicted poorer physical and cognitive function.

Despite the advantages of the longitudinal panel design, it is still subject to nonrandom missing data related to study burnout and health decline. Following multiple cohorts over time via a cross-sequential design can help to distinguish historical and generational changes from intraindividual change. On the other hand, inflammation also can change in a quicker time frame than years and generations in response to daily life stressors, experimental manipulation, and intervention.

## **Ambulatory Measurement, Daily Diary, and Longitudinal Burst Designs**

Inflammatory levels can change from day to day, but because of the expense, little is known about how daily social and environmental challenges affect inflammatory dynamics. Instead, it is more common to relate daily patterns to inflammation assessed in a single clinic visit. For example, in the National Study of Daily Experiences, a study within MIDUS, people whose positive affect decreased more on days when they experienced a stressor compared to nonstressor days also had higher IL-6 levels than did people who were less reactive to daily stressors (Sin, Graham-Engeland, Ong, & Almeida,

## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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2015). As affordable biomarker methods such as blood spots are refined and come into wider use, incorporating inflammatory biomarkers into ecological momentary assessment (EMA) and measurement-burst studies (i.e., the fusion of EMA with panel longitudinal designs) will enable the field to examine the faster dynamics of inflammation and experience in everyday life, as well as how these associations may evolve over the life course.

### **Reactivity Over Time**

In addition to examining resting baseline inflammation, researchers can glean unique information about a person's health from observing how inflammation responds to a challenge. Charting the magnitude of the initial inflammatory response as well as the amount of time required for recovery can indicate a person's efficiency in controlling inflammation, and thus the burden induced by a stressor. As previously mentioned, some proinflammatory cytokines reliably respond to acute psychosocial stress within 30 minutes to 2 hours, depending on the marker. For example, detectable changes in IL-6 started at 40 minutes poststressor and peaked at 90 minutes poststressor or later, while detectable changes in TNF- $\alpha$  arose 31–50 minutes poststressor (Marsland et al., 2017). Recovery occurs thereafter, at varying rates.

Cytokines' diurnal rhythm must be considered in relation to stressor reactivity: The natural circadian rise that begins in the afternoon could be mistaken for a stressor-related increase. Also, illnesses and medications that alter the inflammatory response must be excluded or taken into account systematically in analyses. For example, people with many comorbidities have high levels of chronic inflammation at baseline and, therefore, are limited in the ability to further upregulate inflammation when exposed to a stressor. Both scenarios create interpretational problems for inflammatory reactivity. Nevertheless, reactivity provides a powerful window into the dynamics of a person's inflammatory load and, thus, their long-term risks. Combining measurement of reactivity in the lab with a longitudinal approach can reveal how those short-term dynamics evolve over time.

## Interventions

Because lifespan developmental psychology's culminating objective is to optimize development (Magnusson & Cairns, 1996), researchers also may seek to lower inflammation through an intervention. In this case, inflammation sampling should be timed to the intervention's mechanisms, which may act on the order of days, weeks, months, or longer periods. In women at risk for coronary artery disease, daily aerobic exercise and a high-fiber, low-fat diet reduced CRP and other inflammatory markers after only 2 weeks (Wegge, Roberts, Ngo, & Barnard, 2004). Omega-3 supplementation reduced inflammation in overweight, healthy adults after 4 months (Kiecolt-Glaser et al., 2012). Following 3 months of hatha yoga practice, breast cancer survivors of all ages (27-76) saw significant decreases in inflammatory markers (Kiecolt-Glaser et al., 2014). Similarly, in insomnia-diagnosed breast cancer survivors ages 30-85, 3 months of tai chi and cognitive behavioral therapy reduced stimulated inflammatory responses (Irwin et al., 2014). Thus, inflammation-reducing interventions have shown effects at varying time scales and have been implemented in people of all ages.

## Conclusion

Inflammation is a basic biological process that shapes behavior, health, and longevity. Considering it from a developmental perspective and incorporating inflammatory biomarkers into developmental designs stand to enhance our understanding of both inflammation and lifespan development. Building on studies that have established the importance of early-life experiences for later-life outcomes, future studies should capture both psychosocial experiences and inflammation prospectively, beginning in early childhood. Most research has examined the developmental consistency of stress and inflammation—how risks accumulate. In addition, future studies should seek to capture developmental change—how resilience may interrupt the link between early challenges and later, inflammation-based health problems. The field must examine more closely the dynamics of stressful experiences and inflammation in everyday life. Finally, future studies also should seek to advance our understanding of how inflammatory dynamics shape behavior, sociability, and close relationships over the life course.

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## **Inflammation As a Biomarker Method in Lifespan Developmental Methodology**

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