ANTI-INFLAMMATORIES

Do Anti-Inflammatory Diets and Habits Actually Lower hs-CRP?

How visceral fat loss, dietary fiber fermentation, and circadian meal timing suppress the NLRP3 inflammasome and NF-kappaB signaling in midlife adults.

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A proprietary probiotic strain on a daily sachet or an isolated botanical capsule will not resolve systemic inflammation if visceral adipose tissue, erratic sleep architecture, and nocturnal eating continue to activate innate immune receptors.

Chronic low-grade inflammation—often termed inflammaging—is characterized by a persistent, two- to four-fold elevation in circulating pro-inflammatory cytokines and acute-phase proteins in the absence of overt infection. Unlike acute inflammation, which recruits neutrophils and macrophages to clear pathogens and repair tissue before resolving via specialized pro-resolving mediators (SPMs), chronic sterile inflammation damages vascular endothelium, accelerates atherosclerotic plaque instability, and impairs insulin signaling in skeletal muscle and liver. In clinical practice, the term 'anti-inflammatory' encompasses two distinct categories: pharmaceutical agents (such as non-steroidal anti-inflammatory drugs that inhibit cyclooxygenase enzymes, corticosteroids, and targeted biologics like anti-IL-1beta antibodies) and lifestyle or nutritional interventions that modulate upstream metabolic triggers. While consumer wellness marketing heavily promotes isolated botanical extracts and single-strain gut-brain probiotics to quell systemic inflammation, human randomized controlled trials demonstrate that the reproducible levers in adults aged 40 to 65 are energy balance, reductions in visceral adipose tissue, microbial fermentation of diverse dietary fibers and fermented foods, marine omega-3 fatty acid incorporation into cell membranes, and circadian alignment of sleep and feeding.

What it is

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) and the NLRP3 inflammasome serve as the primary intracellular transcriptional and enzymatic hubs of the human innate immune system; an anti-inflammatory nutritional and behavioral framework is a set of physiological inputs designed to downregulate both pathways. In human cells, NF-kappaB resides in the cytoplasm bound to inhibitory IkappaB proteins. When Toll-like receptors (specifically TLR4 and TLR2) on macrophages, adipocytes, and endothelial cells detect pathogen-associated molecular patterns—such as lipopolysaccharide (LPS) translocating from the gut lumen—or damage-associated molecular patterns—such as oxidized LDL particles, advanced glycation end-products (AGEs), and excess saturated free fatty acids—NF-kappaB translocates to the nucleus. There, it drives the transcription of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), and interleukin-6 (IL-6). Concurrently, intracellular metabolic stress (such as urate crystals, cholesterol crystals, and mitochondrial reactive oxygen species) triggers the assembly of the NLRP3 inflammasome, which activates caspase-1 to cleave pro-IL-1beta and pro-IL-18 into their mature, secreted inflammatory forms. IL-6 travels via the portal and systemic circulation to the liver, where it binds to hepatocyte receptors and activates the JAK/STAT3 pathway, resulting in the release of C-reactive protein (CRP) and fibrinogen into the bloodstream. Anti-inflammatory nutritional and behavioral interventions act by reducing the upstream ligands that trigger TLR4 and NLRP3 (lowering circulating LPS, oxidized lipids, and visceral fat mass) and by supplying bioactive

molecules (such as eicosapentaenoic acid, docosahexaenoic acid, short-chain fatty acids, and polyphenols) that actively resolve the inflammatory cascade.

Why it is used

Prospective epidemiological cohorts, Mendelian randomization studies, and large randomized clinical trials establish that persistently elevated inflammatory biomarkers accelerate vascular disease, insulin resistance, and tissue catabolism in midlife adults. Cardiovascular risk stratification is the primary clinical driver. In large prospective cohorts, individuals with hs-CRP levels at or above 2.0 mg/L have a significantly higher rate of myocardial infarction and ischemic stroke, even when low-density lipoprotein cholesterol (LDL-C) is controlled. Residual inflammatory risk—defined as persistent hs-CRP elevation at or above 2.0 mg/L despite statin therapy—is as strong a predictor of recurrent cardiovascular events as residual cholesterol risk. Beyond the vasculature, chronic elevation of TNF-alpha and IL-6 induces serine phosphorylation of insulin receptor substrate-1 (IRS-1) in human skeletal muscle and hepatocytes, directly impairing GLUT4 translocation and causing peripheral insulin resistance. In the context of musculoskeletal aging, systemic cytokines promote catabolic signaling in skeletal muscle (activating the ubiquitin-proteasome pathway and accelerating sarcopenia) and stimulate osteoclastogenesis, accelerating bone mineral density loss. In the central nervous system, peripheral cytokines cross or signal across the blood-brain barrier to activate microglia, contributing to neuroinflammation, sleep fragmentation, and cognitive decline. However, a critical clinical synthesis must be understood: not every intervention that lowers hs-CRP translates into reduced mortality or disease reversal, and conversely, some lifestyle interventions reduce cardiovascular events before a large drop in systemic hs-CRP is detectable. For example, while the PREDIMED randomized controlled trial (7,447 participants at high cardiovascular risk followed for a median of 4.8 years) demonstrated roughly a 30% relative risk reduction in major cardiovascular events using a Mediterranean diet supplemented with extra-virgin olive oil or nuts, the absolute reductions in hs-CRP and IL-6 in sub-cohorts were modest (roughly 0.3 to 0.6 mg/L), indicating that plaque stabilization, improved endothelial nitric oxide synthase (eNOS) activity, and reduced lipid oxidation operate alongside cytokine reduction.

How it helps

Five distinct, well-characterized molecular pathways verified in human trials and mechanistic studies explain how dietary and behavioral levers suppress systemic cytokine production: 1. Visceral Adipose Tissue Reduction and Adipokine Shift Visceral fat is an active endocrine organ; as adipocytes hypertrophy under caloric excess, they outgrow their capillary blood supply, become hypoxic, and undergo necrosis. This recruits circulating monocytes that differentiate into crown-like structures of M1-polarized pro-inflammatory macrophages. In humans, weight loss of 5% to 10% achieved through sustained caloric deficit shrinks visceral adipocytes, reduces macrophage infiltration, lowers leptin and resistin, and increases adiponectin. Adiponectin binds to AdipoR1 and AdipoR2 receptors in liver and muscle, activating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor alpha (PPAR-alpha), which directly suppresses NF-kappaB activation. In the Look AHEAD trial and systematic reviews of human lifestyle and surgical weight-loss interventions, every 1 kg of weight lost corresponds to a mean decline of approximately 0.13 mg/L in serum hs-CRP. 2. Gut Barrier Integrity, Short-Chain Fatty Acids, and Fermented Foods Consumer marketing frequently claims that a single proprietary probiotic strain on a sachet can heal intestinal permeability, resolve irritable bowel syndrome, and normalize mood via the gut-brain axis. Human evidence does not support these broad claims for isolated retail strains; meta-analyses of probiotic RCTs show high heterogeneity, transient colonization, and no consistent effect size on systemic hs-CRP or IL-6 in healthy or metabolically impaired adults. In contrast, whole-food microbial substrates produce reproducible human effects. When colonic bacteria (such as Faecalibacterium prausnitzii and Roseburia species) ferment diverse soluble fibers and resistant starches, they produce

short-chain fatty acids (SCFAs): acetate, propionate, and butyrate. Shown in human colonic tissue and clinical studies, butyrate serves as the primary fuel for colonocytes, upregulating tight-junction proteins (claudins and occludins) to reduce the paracellular translocation of Gram-negative bacterial lipopolysaccharide (LPS) into the portal vein (metabolic endotoxemia). Butyrate also inhibits histone deacetylases (HDACs) and binds to G-protein-coupled receptors (GPR41, GPR43, and GPR109A) on intestinal regulatory T cells (Tregs), promoting interleukin-10 (IL-10) secretion. Furthermore, a 10-week randomized controlled trial in 36 healthy adults demonstrated that consuming six servings daily of fermented foods (yogurt, kefir, fermented cottage cheese, kimchi, sauerkraut, vegetable brine drinks) significantly increased gut microbiome alpha-diversity and reduced 19 circulating inflammatory proteins, including IL-6, while reducing activation of four immune cell types (effector memory CD4+ T cells, mucosal-associated invariant T cells, classical monocytes, and B cells). 3. Marine Omega-3 Fatty Acids and Specialized Pro-Resolving Mediators (SPMs) Arachidonic acid (an omega-6 polyunsaturated fatty acid abundant in cell membranes) is cleaved by phospholipase A2 and metabolized by COX and lipoxygenase (LOX) enzymes into pro-inflammatory eicosanoids, such as prostaglandin E2 and leukotriene B4, which drive vasodilation, pain, and leukocyte chemotaxis. Consuming marine omega-3 fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fatty fish or purified concentrates—partially displaces arachidonic acid in phospholipid bilayers. EPA and DHA bind to the G-protein-coupled receptor GPR120 on macrophages, activating beta-arrestin-2 to sequester TAK1 and block downstream NF-kappaB and JNK signaling. Crucially, shown in both human plasma lipidomics and tissue studies, EPA and DHA are enzymatic substrates for resolvins (E-series and D-series), protectins, and maresins. These SPMs do not merely block inflammation (which can impair host defense); they actively terminate it by halting neutrophil infiltration and stimulating macrophage efferocytosis (the clearance of cellular debris). 4. Extra-Virgin Olive Oil Polyphenols and Phytochemicals Extra-virgin olive oil contains oleocanthal, a phenolic compound shown in biochemical assays to inhibit COX-1 and COX-2 enzymes in a concentration-dependent manner similar to ibuprofen, though dietary intake achieves mild, chronic modulation rather than acute analgesia. Hydroxytyrosol and oleuropein in olive oil, alongside anthocyanins in berries and sulforaphane in cruciferous vegetables, activate the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2). In human clinical studies, Nrf2 translocation induces phase II antioxidant enzymes—such as heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione S-transferases—which neutralize reactive oxygen species that would otherwise trigger the NLRP3 inflammasome. Curcumin (from Curcuma longa) inhibits NF-kappaB and STAT3 in cell culture and rodent models; while meta-analyses of human RCTs report modest reductions in hs-CRP (roughly 0.5 to 0.8 mg/L in populations with metabolic syndrome or osteoarthritis), unformulated curcumin has less than 1% oral bioavailability due to rapid glucuronidation in the gut and liver, requiring phospholipid complexes or piperine co-administration, which introduces drug-interaction trade-offs. 5. Skeletal Muscle Myokines and Vagal Tone via Sleep and Circadian Timing During acute aerobic or resistance exercise, contracting human skeletal muscle fibers synthesize and release myokines, notably IL-6, completely independent of TNF-alpha. Unlike macrophage-derived IL-6, this acute myokine pulse is anti-inflammatory: in human physiological studies, it stimulates the systemic appearance of IL-1 receptor antagonist (IL-1ra) and IL-10, and inhibits TNF-alpha production. Meta-analyses of exercise training RCTs show that regular training over weeks to months lowers basal resting hs-CRP by roughly 0.3 to 0.7 mg/L. Equally critical is sleep regularity and meal timing. Controlled human inpatient sleep-restriction studies demonstrate that truncating sleep to 4 hours per night for under a week, or shifting feeding windows to biological night (such as eating heavy meals at 1 a.m.), increases sympathetic nervous system outflow, elevates nocturnal cortisol, reduces heart rate variability (HRV), and raises daytime IL-6 and hs-CRP. Consolidating caloric intake to daytime hours and maintaining consistent sleep onset and wake times preserve efferent vagus nerve activity. Acetylcholine released by the vagus nerve binds to alpha-7 nicotinic acetylcholine receptors (alpha7nAChR) on splenic and tissue macrophages, directly inhibiting TNF-alpha release via the cholinergic anti-inflammatory pathway.

Who should try it

Midlife adults aged 40 to 65 who exhibit objective biochemical markers of subclinical inflammation or cardiometabolic dysfunction derive the highest measurable benefit from an anti-inflammatory nutritional and behavioral guide: - Individuals with Cardiometabolic Risk: Adults whose serial fasting blood panels show hs-CRP persistently between 1.5 and 10.0 mg/L (a single hs-CRP reading above 10.0 mg/L typically reflects an acute viral or bacterial infection, trauma, or an autoimmune flare, and must be repeated in two to three weeks before attributing it to metabolic lifestyle factors), especially when paired with elevated Apolipoprotein B (ApoB > 90 mg/dL), elevated triglycerides (> 150 mg/dL), or fasting insulin resistance. - Adults with Central Adiposity or Fatty Liver: Individuals with an elevated waist-to-height ratio (> 0.5) or imaging evidence of metabolic dysfunction-associated steatotic liver disease (MASLD), where visceral and hepatic macrophages drive systemic cytokine spillover. - Adults Experiencing Circadian Disruption: Shift workers or travelers who routinely eat late at night, experience fragmented sleep, and present with concurrent gastrointestinal dysmotility, morning joint stiffness, or depressed heart rate variability. - Osteoarthritis and Musculoskeletal Aging: Adults aged 40 to 65 managing degenerative joint discomfort who want to reduce reliance on chronic oral NSAIDs. Trade-offs, Side Effects, and Contraindications: Lifestyle and nutritional anti-inflammatories carry specific clinical caveats and trade-offs. Rapidly increasing dietary fiber from under 15 grams to over 35 grams per day causes bloating, flatulence, and abdominal cramping in individuals with visceral hypersensitivity or irritable bowel syndrome (IBS); in these cases, low-FODMAP soluble fibers or gradual titration of fermented foods is better tolerated. Fermented foods are high in biogenic amines (tyramine and histamine); individuals with histamine intolerance or those taking monoamine oxidase inhibitors (MAOIs) must avoid or limit them. For concentrated marine omega-3 supplements, large human cardiovascular RCTs (such as REDUCE-IT and STRENGTH, studying over 21,000 combined participants) identified a statistically significant dose-dependent increase in the risk of atrial fibrillation (roughly 1% absolute risk increase in high-risk cardiovascular cohorts taking high-dose prescription omega-3 concentrates), alongside mild antiplatelet effects that require medical supervision if combined with anticoagulants like warfarin or direct oral anticoagulants (DOACs). Concentrated botanical extracts like curcumin combined with piperine inhibit hepatic cytochrome P450 enzymes (specifically CYP3A4) and P-glycoprotein, altering the blood levels of statins, antihypertensives, and immunosuppressants, and carry rare documented case reports of idiosyncratic drug-induced liver injury (DILI). Finally, the opportunity cost is substantial: spending hundreds of dollars monthly on proprietary gut-brain probiotic sachets and botanical stacks diverts financial resources and attention from whole-food quality, sleep architecture, and structured exercise.

Measurements that show improvement

Serial blood biomarkers, lipid ratios, and autonomic physiological metrics tracked over an 8- to 16-week window provide objective verification of whether an anti-inflammatory intervention is working: 1. High-Sensitivity C-Reactive Protein (hs-CRP): The primary clinical marker of hepatic acute-phase response to IL-6. Target direction: decrease. Optimal cardiovascular risk targets are < 1.0 mg/L (ideally < 0.5 mg/L). Because biological variability is high, average two fasting readings taken two weeks apart while free of upper respiratory infections, dental procedures, or unaccustomed eccentric muscle soreness. 2. GlycA (Glycoprotein Acetylation): Measured via nuclear magnetic resonance (NMR) spectroscopy, GlycA quantifies the enzymatic glycosylation of multiple acute-phase proteins (alpha-1-acid glycoprotein, haptoglobin, alpha-1-antitrypsin, alpha-1-antichymotrypsin, and transferrin). Unlike hs-CRP, GlycA exhibits lower intra-individual week-to-week variability and reflects integrated systemic neutrophil and hepatic inflammatory activity. Target direction: decrease toward < 350 umol/L. 3. Omega-3 Index: The combined percentage of EPA and DHA in red blood cell membranes, reflecting dietary intake over the preceding 90 to 120 days. Target direction: increase from a typical starting point of 4% into the target range of 8% to 11%, which correlates with higher endogenous production of resolvins and lower systemic eicosanoid tone. 4. Fasting Insulin, HbA1c, and Triglyceride-to-HDL Ratio: Because TNF-alpha and IL-6 directly

impair insulin signaling and hepatic VLDL metabolism, resolving adipose inflammation lowers fasting insulin (target < 6 to 8 uIU/mL), stabilizes HbA1c (target < 5.3%), and reduces the triglyceride-to-HDL ratio (target < 1.5 when measured in mg/dL). 5. Apolipoprotein B (ApoB) and Liver Enzymes (ALT, AST, GGT): Resolving hepatic steatosis and oxidative stress lowers ApoB (target < 80 mg/dL, or < 60 mg/dL in high-risk individuals) as well as ALT and GGT (target < 25 U/L for men, < 20 U/L for women). Gamma-glutamyl transferase (GGT) specifically tracks intracellular glutathione turnover and hepatic oxidative stress. 6. Overnight Heart Rate Variability (HRV) and Resting Heart Rate (RHR): Tracked via validated wearables during sleep. Eliminating late-night meals (stopping caloric intake 3 to 4 hours before sleep) and alcohol increases root mean square of successive differences (RMSSD, a proxy for vagal tone and cholinergic anti-inflammatory signaling) by roughly 5 to 15 ms and lowers overnight RHR by 3 to 6 bpm within days. 7. Body Composition (DEXA Visceral Adipose Tissue): Rather than scale weight alone, track visceral adipose tissue (VAT) mass or volume via dual-energy X-ray absorptiometry (DEXA). Target direction: decrease toward < 100 cm2 in cross-sectional area (or < 0.5 lbs of VAT mass). Within the LetsGo clinical framework, tracking how hs-CRP, fasting insulin, liver enzymes, and albumin shift in tandem allows physicians to calculate phenotypic biological age (BioAge) and distinguish whether an individual's inflammatory burden stems primarily from visceral adiposity, circadian autonomic stress, or gut barrier dysbiosis.

Products and services

These LetsGo products and services sit next to this subject. They are not a prescription. A link is not evidence that the product causes the change discussed above. - [LetsGo supplement shelf](/supplements) — Bottles LetsGo stocks for members. Read the label before the first order. A link is not a dose. - [LetsGo programmes](/programs) — Coached programmes. Not a clinic menu and not a promise of a result.

Practical takeaways

- Finish caloric intake at least 3 to 4 hours before sleep onset and avoid eating during biological night (such as 1 a.m. during travel) for 14 consecutive days, tracking overnight RHR (target decrease of 3 to 6 bpm) and HRV RMSSD (target increase of 5 to 15 ms).
- Consume 2 to 6 servings daily of unsweetened fermented foods (yogurt, kefir, kimchi, sauerkraut) alongside at least 30 grams of dietary fiber from legumes, oats, seeds, and vegetables for 10 weeks; discontinue any retail probiotic sachet if hs-CRP or gastrointestinal symptoms show no measurable improvement after 8 weeks.
- Replace refined carbohydrates and saturated fat surpluses with 2 to 4 tablespoons of extra-virgin olive oil daily and 2 to 3 servings weekly of fatty fish (salmon, sardines, mackerel, anchovies) over 12 to 16 weeks to raise the red blood cell Omega-3 Index into the 8% to 11% range.
- Reduce total body weight by 5% to 10% over 12 to 24 weeks if waist-to-height ratio exceeds 0.5, combining at least 150 minutes per week of Zone 2 aerobic training with 2 to 3 resistance training sessions to lower DEXA visceral adipose tissue below 100 cm2 and reduce hs-CRP by 0.5 to 1.5 mg/L.
- Measure paired fasting blood panels at starting point and 12 weeks—including hs-CRP (drawn 48 hours after heavy exercise), fasting insulin (target < 8 uIU/mL), ALT/GGT (target < 25 U/L in men, < 20 U/L in women), and ApoB (target < 80 mg/dL)—and repeat any single hs-CRP reading above 10.0 mg/L within 2 weeks to rule out acute infection.

Safety note

A single hs-CRP reading above 10.0 mg/L or new-onset systemic symptoms (unexplained fever, night sweats, unintended weight loss, localized joint swelling, or persistent gastrointestinal bleeding) warrants immediate medical evaluation to rule out acute infection, autoimmune disease, or malignancy rather than lifestyle

self-management. Consult a physician before initiating concentrated omega-3 or botanical extracts (such as curcumin) if you take anticoagulants, antiplatelet agents, antihypertensives, or medications metabolized by hepatic CYP3A4 enzymes.

Disclaimer

This educational explainer is for informational purposes only and does not constitute medical advice, clinical diagnosis, or a prescription. Dietary, behavioral, and supplemental interventions should be tailored to your medical history and laboratory findings in consultation with a qualified healthcare professional.

Reducing chronic systemic inflammation does not require exotic botanical stacks or unverified gut-brain probiotic strains. Human clinical trials and mechanistic physiology point to a clear hierarchy of intervention: shrinking visceral adipose tissue through sustained energy balance, supplying the colonic microbiome with diverse fibers and fermented foods, increasing membrane EPA and DHA levels to generate pro-resolving lipid mediators, performing regular skeletal muscle contraction, and protecting circadian sleep and feeding windows. By tracking objective markers like hs-CRP, GlycA, fasting insulin, and overnight HRV, adults can systematically lower their inflammatory burden and mitigate the downstream vascular and metabolic risks of aging.