

## Review Article

# Chronic stress, allostatic load and multisystem disease: mapping mechanisms and evidence for lifestyle interventions – a narrative review

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## ABSTRACT

Chronic psychological stress is linked to cardiovascular, metabolic, immune-mediated, gastrointestinal, and depressive disorders. Allostatic load (AL), defined as the cumulative physiological cost of repeated or sustained adaptation, serves as the primary framework for explaining these associations. Lifestyle interventions, including yoga, meditation, physical activity, sleep improvement, dietary modification, and social support, are widely recommended for stress-related health issues. It remains uncertain whether these interventions influence multisystem AL or only affect individual biomarkers and symptoms. This narrative review is based on a structured, though non-systematic, PubMed/MEDLINE search that prioritised systematic reviews, meta-analyses, randomised trials, and large cohort studies. The review summarises neural, neuroendocrine, autonomic, inflammatory, metabolic, gut-brain, cellular, and epigenetic pathways through which stress becomes biologically embedded, distinguishing mechanisms established in humans from those inferred primarily from animal or cross-sectional studies. Intervention evidence is then mapped against the five biomarkers of a recently proposed consensus AL index (C-reactive protein [CRP], resting heart rate, high-density lipoprotein cholesterol, waist-to-height ratio, and glycated haemoglobin) as well as clinical endpoints. Physical activity and a Mediterranean-style diet have the strongest support across these domains and clinical outcomes. Meditation, yoga, and slow breathing yield small-to-moderate improvements in distress and in certain cardiometabolic and autonomic markers, while cognitive behavioural therapy demonstrates clinical-endpoint evidence in insomnia and coronary heart disease. Few randomised trials have assessed composite AL, and their findings are inconsistent. No intervention has yet demonstrated disease prevention through reduction of AL. Standardised AL measurement in adequately powered trials represents the most important next step.

**Keywords:** Allostasis, Allostatic load, Psychological stress, Hypothalamic-pituitary-adrenal axis, Lifestyle medicine, Yoga

## INTRODUCTION

Stress is a frequently discussed but imprecisely used concept in medicine. The World Health Organization describes it as a state of worry or mental tension caused by a difficult situation, whereas physiology has, since Selye, used the term for the organism's response to demands that threaten its internal stability.<sup>1-3</sup> The meanings are

connected: the appraisal of threat that produces worry also activates neural, endocrine and immune systems whose short-term actions are protective but whose prolonged activation can be damaging.<sup>4</sup> Cohort studies link chronic psychosocial stress with coronary heart disease, type 2 diabetes, autoimmune disease and depression, although effect sizes are generally modest.<sup>5-8</sup>

The AL model, formulated by McEwen and Stellar, proposes that these associations reflect cumulative "wear and tear" across several regulatory systems rather than the action of any single hormone.<sup>9</sup> Measured as a composite of neuroendocrine, cardiovascular, metabolic and inflammatory biomarkers, higher AL is associated with poorer health and with mortality.<sup>10-12</sup> Its appeal is that it seems to identify a measurable, modifiable stage between stress exposure and disease, but that appeal has run ahead of the evidence. Lifestyle measures are often recommended to "reduce allostatic load", but most trials measure a single biomarker such as cortisol or CRP, or self-reported stress. A scoping review in 2020 identified only six intervention studies that used composite AL as an outcome, and these selected and scored biomarkers inconsistently.<sup>13</sup> Separately, an individual participant data meta-analysis of 13 cohorts has proposed a brief consensus AL index based on five routinely available biomarkers.<sup>14</sup> To our knowledge, no review has used such an index to ask which lifestyle interventions act on each AL component, and how that evidence relates to clinical outcomes.

This review therefore summarises the mechanisms through which chronic stress becomes biologically embedded, with the strength of human evidence for each; identifies the diseases most strongly linked to stress; and maps the evidence for lifestyle and behavioural interventions against AL domains and clinical endpoints, separating demonstrated effects from extrapolation.

## LITERATURE SEARCH APPROACH

This is a narrative review written with reference to the Scale for the Assessment of Narrative Review Articles (SANRA).<sup>15</sup> It is not systematic: no protocol was registered, selection was not duplicated, and no formal risk-of-bias assessment or meta-analysis was performed. PubMed/MEDLINE was searched in October 2026, combining "allostatic load", "allostasis", "psychological stress" or "chronic stress" with terms for mechanisms ("hypothalamic-pituitary-adrenal axis", "glucocorticoid resistance", "inflammation", "heart rate variability", "mitochondria", "telomere", "epigenetic", "adverse childhood experiences", "prenatal stress"), diseases ("cardiovascular disease", "type 2 diabetes", "autoimmune disease", "irritable bowel syndrome", "depression") and interventions ("yoga", "meditation", "mindfulness", "breathing", "exercise", "sleep", "insomnia", "Mediterranean diet", "social support", "cognitive behavioural therapy", "massage", "naturopathy"). Intervention studies were sought by combining "allostatic load" with "intervention", "trial", "lifestyle", "modifiable" or "reduction", without date limits. Reference lists of key reviews were examined. Human studies in English were preferred; animal studies are cited only to illustrate mechanisms and are identified as such. Evidence was prioritised as follows: meta-analyses of randomised controlled trials (RCTs), individual RCTs, meta-analyses of prospective cohorts, large cohorts, then mechanistic studies; seminal conceptual papers were retained

regardless of age. Bibliographic details were checked against PubMed records.

## CONCEPTS: STRESSORS, APPRAISAL AND THE STRESS RESPONSE

Three distinctions are central to understanding stress. First, the stressor (an actual or perceived challenge) is separate from the stress response.<sup>3</sup> Second, the response depends on appraisal: in the transactional model of Lazarus and Folkman, a situation becomes stressful when it is judged threatening and the available coping resources are judged insufficient,<sup>16</sup> explaining why the same event elicits different responses in different people. Third, duration matters. Acute responses mobilise energy and redistribute immune cells in ways that favour short-term survival; chronic stress (sustained or frequently repeated stressors, or failure to terminate the response) is the condition consistently linked to disease.<sup>4,17</sup>

The distinction between "eustress" and "distress", and the inverted-U relation between arousal and performance, are useful teaching heuristics but poorly operationalised in clinical research. A more defensible form of the idea is hormesis: low or intermittent doses of a stressor, of which exercise is the clearest example, can induce adaptive cellular responses that increase resilience, whereas high or sustained doses cause damage.<sup>18</sup> Likewise, the categories of positive, tolerable and toxic childhood stress mainly describe the buffering role of supportive relationships, not distinct biological states.<sup>19</sup>

Selye's general adaptation syndrome (alarm, resistance, exhaustion) remains historically important,<sup>2</sup> but exhaustion is no longer understood as depletion of adrenal hormones; contemporary models emphasise altered hormone rhythm, receptor sensitivity and feedback.<sup>20</sup> This matters clinically because the popular diagnosis of "adrenal fatigue" has no valid evidence base.<sup>21</sup>

## CENTRAL AND PERIPHERAL STRESS CIRCUITRY

Stress perception depends on distributed networks rather than the hierarchical "triune" brain often used in teaching. The amygdala detects threat and drives autonomic and endocrine activation; the hippocampus and medial prefrontal cortex supply context and inhibition; and brainstem nuclei such as the locus coeruleus drive arousal.<sup>22,23</sup> These converge on the hypothalamic paraventricular nucleus (PVN) and preganglionic autonomic neurons. High catecholamine and glucocorticoid levels impair prefrontal function, so sustained stress can weaken top-down regulation, with relevance to anxiety and health behaviour.<sup>24</sup>

Two effector limbs operate on different time scales. The sympathetic-adrenal-medullary (SAM) system responds within seconds, releasing noradrenaline and adrenaline, while vagal activity is withdrawn; reduced high-frequency heart rate variability (HRV) is among the most consistent

physiological correlates of psychological stress in human studies.<sup>25</sup> The hypothalamic-pituitary-adrenal (HPA) axis responds over minutes: corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the PVN stimulate pituitary adrenocorticotrophic hormone (ACTH), which drives adrenal cortisol secretion. Cortisol acts through mineralocorticoid and glucocorticoid receptors, limits its own secretion through negative feedback, and is secreted in ultradian pulses superimposed on a circadian rhythm that peaks after waking.<sup>20</sup> Effects on reproductive, growth and thyroid axes are less well characterised in human disease and are not considered here.

## ALLOSTASIS AND ALLOSTATIC LOAD

Whereas homeostasis maintains essential variables within narrow limits, allostasis describes stability achieved through change: the anticipatory adjustment of blood pressure, glucose, immune activity and behaviour to predicted demands.<sup>9</sup> AL is the cost of this adaptation when repeated, prolonged or poorly regulated. McEwen described four patterns: repeated activation; failure to habituate; failure to shut off the response; and inadequate responses that allow other systems, such as inflammation, to overreact.<sup>4</sup> When demands exceed coping resources, "allostatic overload" has been proposed, with clinimetric criteria.<sup>11</sup>

Measurement is the model's main weakness. The original MacArthur index summed ten biomarkers, including blood pressure, waist-hip ratio, lipids, glycated haemoglobin (HbA1c), urinary cortisol and catecholamines, and predicted cardiovascular disease and functional decline in older adults.<sup>10</sup> Later studies have used from a few to more than twenty markers with varying cut-offs. A meta-analysis of 17 cohort studies found that high AL was associated with all-cause mortality (hazard ratio [HR] 1.22, 95% confidence interval [CI] 1.14-1.30) and cardiovascular mortality (HR 1.31, 1.10-1.57), but heterogeneity exceeded 90% in most pooled estimates.<sup>12</sup> McCrory and colleagues analysed 40 biomarkers across 12 physiological systems in 67,126 participants and found that a 5-item index of CRP, resting heart rate, high-density lipoprotein cholesterol (HDL-C), waist-to-height ratio and HbA1c predicted mortality as well as, or better than, longer sets.<sup>14</sup>

This index has a rarely acknowledged implication: most of its components are conventional cardiometabolic risk factors, so a fall in AL after an intervention may reflect cardiometabolic improvement rather than a specific effect on stress physiology. It also omits direct HPA-axis measures.

## MECHANISMS LINKING CHRONIC STRESS TO MULTISYSTEM DYSREGULATION

The main pathways, and the strength of human evidence for each, are summarised in Table 1.

### *Neuroendocrine dysregulation*

With prolonged stress, pituitary drive shifts from CRH towards AVP, and cortisol can stay raised through greater adrenal sensitivity and reduced cortisol metabolism even as ACTH normalises.<sup>20</sup> Sustained hypercortisolaemia is not typical in community samples; a more consistent pattern is a flattened diurnal profile, and in a meta-analysis of 80 studies, flatter diurnal cortisol slopes were associated with poorer mental and physical health (average  $r=0.147$ ), most strongly for immune and inflammatory outcomes ( $r=0.288$ ).<sup>26</sup>

### *Glucocorticoid resistance and inflammation*

Prolonged stress can reduce immune-cell sensitivity to glucocorticoids. In parents of children with cancer, the capacity of a synthetic glucocorticoid to suppress interleukin-6 (IL-6) production in vitro was diminished,<sup>27</sup> and in viral-challenge studies, glucocorticoid receptor resistance associated with a recent long-term stressor predicted greater local pro-inflammatory cytokine production and susceptibility to developing a cold.<sup>28</sup> This helps explain how raised cortisol and low-grade inflammation coexist. Acute stress can transiently enhance immunity, whereas chronic stress tends to suppress protective immunity and promote inflammation.<sup>17,29</sup> In mice, chronic variable stress increased sympathetic signalling in bone marrow and inflammatory leukocyte production; stressed humans in the same study had higher neutrophil and monocyte counts.<sup>30</sup> In a human positron emission tomography study of 293 adults, resting amygdalar activity was associated with bone-marrow activity, arterial inflammation and subsequent cardiovascular events, consistent with, but not proof of, a brain-marrow-artery pathway.<sup>31</sup>

### *Metabolic pathways*

Cortisol and catecholamines increase hepatic glucose output, lipolysis and insulin resistance, and sustained glucocorticoid exposure favours visceral adiposity. Restricting sleep to 4 hours a night for 6 nights in healthy young men reduced glucose tolerance and raised evening cortisol and sympathetic activity.<sup>32</sup> Health behaviours are often assumed to mediate the link between stressors and AL, but a systematic review of observational studies found only partial and inconsistent support.<sup>33</sup>

### *Gut-brain axis*

The gastrointestinal tract is both a target and a source of stress signals. In healthy volunteers, a public-speaking stressor increased small-intestinal permeability, but only in those whose cortisol rose; peripheral CRH reproduced the effect and a mast-cell stabiliser blocked it.<sup>34</sup> Increased permeability and stress-related shifts in the microbiota could raise systemic inflammation and signal back to the brain through vagal, immune and microbial-metabolite pathways, although most evidence for these feedback loops comes from animal models.<sup>35,36</sup> The gut-brain axis is

therefore a plausible, partly human-supported contributor to the inflammatory component of AL.

### Cellular stress responses

Stress can alter mitochondrial function ("mitochondrial allostatic load"), but in a systematic review the experimental evidence came entirely from male laboratory animals, and the six human studies were observational with indirect markers.<sup>37</sup> Caregiving stress was associated with shorter leukocyte telomeres in an influential early study,<sup>38</sup> but a later meta-analysis of 22 studies found only a very small association between perceived stress and telomere length ( $r=-0.06$ ), which may be inflated by publication bias.<sup>39</sup>

### Developmental programming and epigenetic mechanisms

Exposure during sensitive periods may calibrate stress systems for life. Prenatal maternal stress is associated with altered offspring neurodevelopment, HPA and autonomic function, and behavioural and psychiatric problems, though confounding by shared genes and postnatal

environment is hard to exclude.<sup>40</sup> Adverse childhood experiences (ACEs) show graded associations with adult ischaemic heart disease, cancer, chronic lung disease and depression,<sup>41</sup> and in a meta-analysis of 37 studies, four or more ACEs carried odds ratios of two to three for heart disease and cancer, and above three for mental ill health.<sup>42</sup> Epigenetic mechanisms are a plausible route. In rats, variation in maternal care altered methylation of the hippocampal glucocorticoid receptor gene promoter;<sup>43</sup> in post-mortem human hippocampus, childhood abuse was associated with increased methylation of the glucocorticoid receptor (NR3C1) promoter;<sup>44</sup> and childhood trauma interacts with FKBP5 genotype to produce allele-specific demethylation that alters glucocorticoid sensitivity.<sup>45</sup> Beyond single genes, cumulative lifetime stress, but not childhood maltreatment or current stress alone, predicted accelerated DNA-methylation ("epigenetic clock") ageing in 392 adults, and many clock sites lie within glucocorticoid response elements, linking epigenetic ageing to glucocorticoid signalling.<sup>46</sup> These coherent findings derive largely from animal models, small post-mortem samples or specific genotypes, and do not yet justify clinical epigenetic testing.

**Table 1: Principal pathways linking chronic stress to multisystem dysregulation, and strength of human evidence.**

| Pathway                                            | Key features                                                                                        | Principal evidence                                                                                                                      | Evidence status                                            |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|
| <b>HPA-axis dysregulation</b>                      | Shift towards AVP drive; flattened diurnal cortisol slope; altered feedback                         | Human mechanistic studies; meta-analysis of 80 observational studies linking flatter slopes with poorer health <sup>20,26</sup>         | Established association; causal direction uncertain        |
| <b>Sympathetic activation and vagal withdrawal</b> | Raised catecholamines; reduced high-frequency HRV                                                   | Human laboratory and ambulatory studies; meta-analysis of HRV reactivity <sup>25</sup>                                                  | Established in humans                                      |
| <b>Glucocorticoid resistance</b>                   | Reduced immune-cell sensitivity to cortisol; failure to restrain IL-6 and other cytokines           | Human observational and viral-challenge studies <sup>27,28</sup>                                                                        | Supported in humans; limited replication                   |
| <b>Inflammation and myelopoiesis</b>               | Sympathetic stimulation of bone marrow; monocytosis, neutrophilia; arterial inflammation            | Mouse experiments; human cross-sectional data and one imaging cohort ( $n=293$ ) <sup>30,31</sup>                                       | Partly animal; human data associative                      |
| <b>Metabolic dysregulation</b>                     | Insulin resistance, visceral adiposity, dyslipidaemia; behavioural pathways                         | Experimental sleep restriction in humans; observational studies of behavioural mediation <sup>32,33</sup>                               | Components established; behavioural mediation inconsistent |
| <b>Gut-brain axis</b>                              | Increased intestinal permeability (CRH, mast cells); microbiota shifts; vagal and immune signalling | Human experimental stress study (permeability); microbiota evidence mostly from animals <sup>34,35</sup>                                | Partly human; microbiota largely animal                    |
| <b>Mitochondrial and oxidative stress</b>          | Altered mitochondrial function and energetics                                                       | Experiments almost entirely in male laboratory animals; six observational human studies <sup>37</sup>                                   | Largely animal; proposed in humans                         |
| <b>Telomere attrition</b>                          | Shorter leukocyte telomeres                                                                         | Meta-analysis: very small association ( $r=-0.06$ ), possible publication bias <sup>39</sup>                                            | Weak                                                       |
| <b>Developmental programming and epigenetics</b>   | NR3C1 and FKBP5 methylation; epigenetic-clock ageing; programmed HPA reactivity                     | Rat models; post-mortem and genotype-specific human studies; ACE cohorts; cohort data on accelerated epigenetic ageing <sup>42-46</sup> | Biologically plausible; not clinically actionable          |

\*ACE-adverse childhood experiences; AVP-arginine vasopressin; FKBP5-FK506-binding protein 5; HPA-hypothalamic-pituitary-adrenal; HRV-heart rate variability; IL-6-interleukin-6; CRH-corticotropin-releasing hormone and NR3C1-glucocorticoid receptor gene.

## CHRONIC STRESS AND DISEASE: WHERE THE EVIDENCE IS STRONGEST

### Cardiovascular disease

In an individual participant data meta-analysis of 13 European cohorts including 197,473 people, job strain was associated with incident coronary heart disease (HR 1.23, 95% CI 1.10-1.37).<sup>6</sup> In the INTERHEART case-control study from 52 countries, permanent work stress roughly doubled the odds of myocardial infarction.<sup>47</sup> In Swedish registers, stress-related psychiatric disorders were associated with cardiovascular disease in sibling-controlled analyses (HR 1.64 in the first year after diagnosis and 1.29 thereafter).<sup>48</sup> Acute stress also triggers events; in case-crossover studies the pooled relative risk of acute coronary syndrome after stress is about 2.5.<sup>49</sup> Adult stress appears weaker than smoking or hypertension as a risk factor but important as a trigger and prognostic factor.<sup>50</sup>

### Type 2 diabetes

Prospective studies link work stress, depression, trauma and emotional stress to incident type 2 diabetes and to poorer glycaemic control, through neuroendocrine and behavioural pathways.<sup>7</sup>

### Immune-mediated disease

In a Swedish cohort of 106,464 people with stress-related disorders, the risk of subsequent autoimmune disease was increased (HR 1.36, 95% CI 1.33-1.40), with consistent sibling-based estimates.<sup>8</sup> A UK Biobank analysis of 186,310 participants found that the highest AL quartile was associated with greater incidence of several immune-mediated inflammatory diseases, partly attenuated by physical activity, although the authors' causal interpretation of observational data warrants caution.<sup>51</sup>

### Gastrointestinal disorders

Through the mechanisms above, together with altered motility and visceral sensitivity, stress is implicated in irritable bowel syndrome and in the course of inflammatory bowel disease.<sup>36</sup>

### Depression

In a population-based twin study, the odds of major depression in the month of a stressful life event were 5.64, but about one-third of the association was non-causal, reflecting the tendency of predisposed individuals to encounter high-risk environments.<sup>52</sup> The relationship is bidirectional and is shaped by earlier life stress.<sup>53</sup>

Two qualifications apply throughout. Most evidence is observational, so confounding and reverse causation cannot be excluded; and most people exposed to chronic stress do not develop these diseases: genes, early

experience, social resources and coping contribute to resilience, an active biological process rather than mere absence of vulnerability.<sup>54</sup>

## LIFESTYLE AND BEHAVIOURAL INTERVENTIONS: AN EVIDENCE MAP

### A stage-based framework

Figure 1 classifies interventions by where they act on the pathway from exposure to disease: stressor exposure (social and occupational conditions); appraisal and coping (cognitive behavioural therapy [CBT], mindfulness); the acute mediator response (slow breathing, yoga, meditation); recovery (sleep); and downstream biological targets (physical activity, diet, adiposity). This synthesis tool, not a validated causal model, shows that an intervention acting only downstream could lower AL without changing exposure or appraisal. Table 2 maps each intervention against the consensus AL biomarkers, HPA and autonomic markers, composite AL and clinical endpoints.<sup>14</sup>

### Meditation and mindfulness

In a systematic review of RCTs with active controls, mindfulness programmes gave moderate-strength evidence of small improvements in anxiety (effect size 0.38 at 8 weeks), depression (0.30) and pain, low-strength evidence for stress, and no superiority over active treatments.<sup>55</sup> Meta-analysis of 45 RCTs with active controls found reductions in cortisol, CRP, blood pressure, heart rate, triglycerides and tumour necrosis factor- $\alpha$ .<sup>56</sup> Effects on immune and cellular-ageing markers remain tentative.<sup>57</sup>

### Yoga

Against active controls, practices including postures (asanas) were associated with lower cortisol, ambulatory systolic blood pressure and resting heart rate, higher HRV, and lower fasting glucose and lipids in a meta-analysis of 42 heterogeneous RCTs.<sup>58</sup> In a meta-analysis of 44 RCTs, yoga improved systolic blood pressure (mean difference -5.85 mmHg), heart rate, waist circumference, HDL-C (+2.94 mg/dl), triglycerides and HbA1c (-0.45%) relative to usual care, but most trials had high or unclear risk of bias.<sup>59</sup> Yoga appears as safe as usual care and exercise.<sup>60</sup> These effects involve four of the five consensus AL components or close proxies, but no yoga trial has used cardiovascular events or diabetes incidence as outcomes.

### Slow breathing

A meta-analysis of breathwork RCTs found a small-to-moderate reduction in self-reported stress (Hedges'  $g$  -0.35) in trials mostly at moderate risk of bias,<sup>61</sup> and a meta-analysis of 223 studies showed that voluntary slow breathing increases vagally mediated HRV during and after practice.<sup>62</sup> Effects on the other AL markers are unknown.

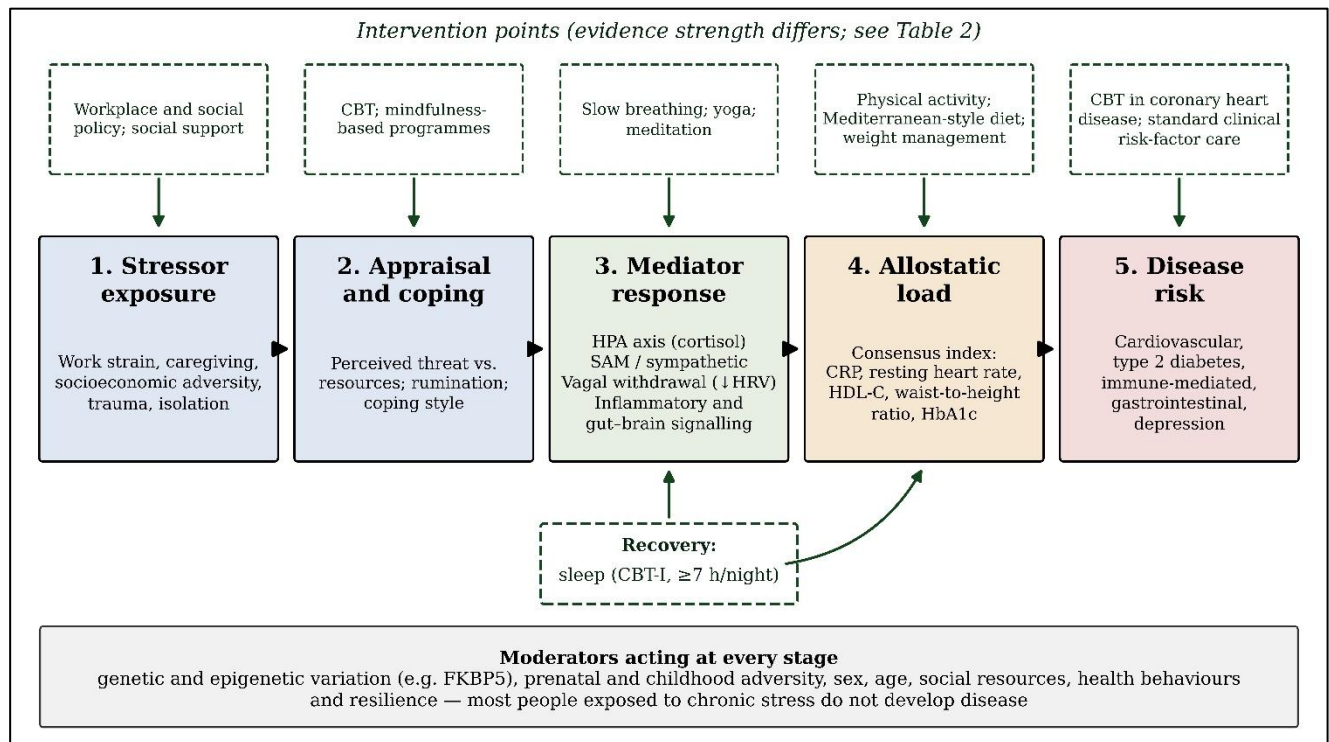


**Figure 1: Stage-based framework linking chronic stress exposure to AL and disease, with proposed intervention points.**

\*Stressor exposure is filtered by appraisal and coping and activates neuroendocrine, autonomic and inflammatory mediators; repeated or prolonged activation contributes to AL, summarised here by the five-biomarker consensus index, which is in turn associated with disease risk.<sup>14</sup> Dashed boxes show the stage at which each intervention is proposed to act; strength of evidence differs substantially between interventions (Table 2). Sleep is shown as a recovery process influencing both mediator activity and AL. Moderators act at every stage, and illness can itself become a stressor (not shown). The framework is an organising tool and has not been empirically validated. Original figure prepared by the authors. CBT-cognitive behavioural therapy; CBT-I, CBT for insomnia; CRP-C-reactive protein; HbA1c-glycated haemoglobin; HDL-C-high-density lipoprotein cholesterol; HPA-hypothalamic-pituitary-adrenal; HRV-heart rate variability; SAM-sympathetic-adrenal-medullary.

### Physical activity

Physical activity has medium effects on depression, anxiety and distress, with larger antidepressant effects at higher intensity.<sup>63,64</sup> Exercise training lowers CRP (effect size 0.26, with a smaller but significant effect even without weight loss), reduces resting heart rate, modestly raises HDL-C (2.53 mg/dl) and, as structured training, lowers HbA1c in type 2 diabetes (-0.67%).<sup>65-68</sup> It also has the clearest randomised evidence on composite AL: in the FIERCE trial, 6 months of aerobic exercise lowered AL versus wait-list control in 213 inactive postmenopausal Black women with obesity.<sup>69</sup> Its links with lower morbidity and mortality underpin the World Health Organization recommendation of 150-300 minutes of moderate-intensity activity weekly.<sup>70</sup>

### Sleep

Adults are advised to sleep at least 7 hours a night.<sup>71</sup> In cohort studies sleep disturbance is associated with higher CRP and IL-6, although experimental sleep deprivation has not consistently raised inflammatory markers.<sup>72</sup> CBT for insomnia (CBT-I) improves sleep onset and night-time

wakefulness, and in older adults it reduced odds of high CRP at 16 months versus a sleep seminar control (odds ratio 0.26).<sup>73,74</sup> Sleep is a plausible but under-tested AL target.

### Nutrition

Dietary improvement modestly reduces depressive symptoms, and Mediterranean dietary patterns reduce high-sensitivity CRP and IL-6.<sup>75-77</sup> In the corrected 2018 PREDIMED analysis, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced major cardiovascular events (HR 0.69 and 0.72, respectively).<sup>78</sup> This clinical-endpoint benefit has not been shown to operate through stress pathways.

### Gut-directed approaches

In a meta-analysis of 34 controlled trials, probiotics had small effects on depression ( $d=-0.24$ ) and anxiety ( $d=-0.10$ ), and prebiotics had none; no trial has measured composite AL.<sup>79</sup> In irritable bowel syndrome, CBT and gut-directed hypnotherapy reduced the risk of persistent symptoms (relative risk about 0.6-0.7), although trial risk

of bias was high and the efficacy is probably overestimated.<sup>80</sup>

### Social connection and psychological therapy

In a meta-analysis of 148 prospective studies, stronger social relationships were associated with a 50% greater likelihood of survival (odds ratio 1.50), but trials that increase social support and measure AL are lacking.<sup>81</sup> Psychosocial interventions, most reliably CBT, improve immune function, including pro-inflammatory markers.<sup>82</sup> In coronary heart disease, the SUPRIM trial found that group CBT focused on stress management reduced recurrent cardiovascular events by 41% over a mean of 94 months, and a Cochrane review found a reduction in cardiac mortality (risk ratio 0.79) but not in total mortality, on low-quality evidence.<sup>83,84</sup>

### Naturopathic modalities

Evidence for common naturopathic modalities is limited. Massage therapy has very small effects on cortisol that are mostly indistinguishable from zero, despite benefits for

anxiety and pain; forest bathing is associated with short-term reductions in salivary cortisol, but data are limited and expectancy effects may contribute.<sup>85,86</sup> We found no RCTs that measured composite AL after hydrotherapy, therapeutic fasting or residential yoga-and-naturopathy programmes. These modalities are unproven with respect to AL, although integrated programmes often include components (exercise, diet, yoga, sleep regulation) that do have supporting evidence.

### Trials using composite AL

Besides FIERCE, a cluster-randomised church-based diabetes prevention programme was followed by a small fall in AL, but both arms were active, so the change cannot be attributed to either.<sup>87</sup> An 18-month church-based trial found AL reductions in both arms, without a group-by-time interaction.<sup>88</sup> The largest mind-body trial to date randomised 211 chronically stressed but otherwise healthy adults to 8 weeks of meditation, yoga or stress education and found no between-group differences in any psychological, AL or gene-expression outcome, possibly because of floor effects in a healthy sample.<sup>89</sup>

**Table 2: Evidence map of lifestyle and behavioural interventions against AL domains and clinical endpoints.**

| Intervention                       | Consensus AL biomarkers <sup>a</sup>                                          | HPA and autonomic markers                                                                       | Composite AL in RCTs                                           | Clinical or symptom endpoints                                                                                                 | Overall rating <sup>b</sup>                                           |
|------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| <b>Physical activity</b>           | CRP↓, RHR↓, HDL-C↑, HbA1c↓ (meta-analyses) <sup>65-68</sup>                   | Not summarised here                                                                             | Reduced vs wait-list in one RCT (n=213) <sup>69</sup>          | Depression, anxiety, distress improved (meta-analyses); lower morbidity and mortality underpin guidelines <sup>63,64,70</sup> | Credible                                                              |
| <b>Mediterranean-style diet</b>    | hs-CRP↓ (meta-analysis) <sup>77</sup>                                         | Not established                                                                                 | No RCT identified                                              | Major cardiovascular events↓ (PREDIMED); depressive symptoms↓ (small) <sup>75,76,78</sup>                                     | Credible for cardiovascular outcomes; stress-specific effect unproven |
| <b>Yoga</b>                        | RHR↓, HDL-C↑, waist↓, HbA1c↓ (meta-analysis; high risk of bias) <sup>59</sup> | Cortisol↓, HRV↑ vs active control (heterogeneous) <sup>58</sup>                                 | No difference vs active control (one RCT, n=211) <sup>89</sup> | No trials with hard endpoints; safety comparable to exercise <sup>60</sup>                                                    | Moderate for biomarkers; preliminary for AL                           |
| <b>Meditation and mindfulness</b>  | CRP↓, heart rate↓ vs active control (meta-analysis) <sup>56</sup>             | Cortisol↓ (some subtypes) <sup>56</sup>                                                         | No difference vs active control (one RCT, n=211) <sup>89</sup> | Small improvements in anxiety, depression and pain; low evidence for stress <sup>55</sup>                                     | Moderate for symptoms; preliminary for AL                             |
| <b>Slow breathing</b>              | Not assessed                                                                  | Vagally mediated HRV↑ (meta-analysis) <sup>62</sup>                                             | None identified                                                | Small reduction in self-reported stress <sup>61</sup>                                                                         | Preliminary                                                           |
| <b>Sleep (CBT-I)</b>               | CRP↓ in one RCT of older adults <sup>74</sup>                                 | Sleep restriction raises evening cortisol and sympathetic activity (experimental) <sup>32</sup> | None identified                                                | Improved sleep onset and wakefulness (meta-analysis) <sup>73</sup>                                                            | Credible for insomnia; preliminary for AL                             |
| <b>Psychological therapy (CBT)</b> | Pro-inflammatory markers↓ (meta-analysis of psychosocial RCTs) <sup>82</sup>  | Not summarised here                                                                             | None identified                                                | Recurrent cardiovascular events↓ (one RCT); cardiac mortality↓ (low-quality evidence) <sup>83,84</sup>                        | Moderate                                                              |

Continued.

| Intervention                                                      | Consensus AL biomarkers <sup>a</sup> | HPA and autonomic markers                                   | Composite AL in RCTs | Clinical or symptom endpoints                                                                                                                  | Overall rating <sup>b</sup>                         |
|-------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| <b>Gut-directed approaches</b>                                    | Not assessed                         | Not established                                             | None identified      | Probiotics: small effects on depression and anxiety; IBS symptoms↓ with CBT and gut-directed hypnotherapy (high risk of bias) <sup>79,80</sup> | Preliminary (probiotics); credible for IBS symptoms |
| <b>Social connection</b>                                          | Not established                      | Not established                                             | None identified      | Higher survival with stronger social relationships (observational) <sup>81</sup>                                                               | Observational only                                  |
| <b>Massage</b>                                                    | Not assessed                         | No meaningful cortisol effect (meta-analysis) <sup>85</sup> | None identified      | Benefits for anxiety and pain reported <sup>85</sup>                                                                                           | Unproven for AL                                     |
| <b>Forest bathing</b>                                             | Not assessed                         | Short-term salivary cortisol↓ (limited data) <sup>86</sup>  | None identified      | None identified                                                                                                                                | Preliminary                                         |
| <b>Hydrotherapy, therapeutic fasting, residential naturopathy</b> | No relevant trials identified        | No relevant trials identified                               | None identified      | Not assessed in this review                                                                                                                    | Unproven                                            |

<sup>a</sup>Consensus index of McCrory et al.: CRP, resting heart rate, HDL-C, waist-to-height ratio and HbA1c; waist circumference is shown where waist-to-height ratio was not reported. <sup>b</sup>Authors' qualitative judgement based on design, consistency and directness of the cited evidence; not a formal GRADE assessment. ↑, increase; ↓, decrease; AL-allostatic load; CBT-cognitive behavioural therapy; CBT-I-CBT for insomnia; CRP-C-reactive protein; HbA1c-glycated haemoglobin; HDL-C-high-density lipoprotein cholesterol; HPA-hypothalamic-pituitary-adrenal; HRV-heart rate variability; IBS-irritable bowel syndrome; hs-CRP-high-sensitivity CRP; RCT-randomised controlled trial; RHR-resting heart rate.

## CRITICAL DISCUSSION AND IMPLICATIONS

Three conclusions emerge. The mechanistic case for multisystem effects of chronic stress is strong, but popular explanations such as cortisol "exhaustion" are unsupported. Evidence that lifestyle interventions improve individual AL components is reasonably good for physical activity, Mediterranean-style diet and yoga, more modest for meditation and breathing, and preliminary for sleep. Evidence on composite AL is sparse and inconsistent, and no intervention has been shown to prevent disease by lowering AL.

Biomarker change is not health benefit. A surrogate endpoint is valid only if an intervention's effect on it reliably predicts the effect on the clinical outcome, a test several established biomarkers have failed.<sup>90</sup> AL has not been validated in this sense; its association with mortality in cohorts does not show that lowering it will reduce mortality. Because the consensus index is dominated by cardiometabolic markers, lowering waist-to-height ratio and HbA1c will reduce AL regardless of stress physiology; conversely, meditation may change HRV or cortisol without moving an index that contains neither.

Clinically, interventions should be chosen on the strength of their direct evidence. Physical activity and Mediterranean-style diet have support across AL domains and clinical outcomes; CBT has evidence in insomnia and recurrent cardiac events; and yoga, meditation and slow breathing are reasonable low-risk adjuncts for distress and

some cardiometabolic and autonomic markers. Claims that yoga or naturopathy "reverse allostatic load" are not supported by current evidence. Integrative programmes combining evidence-based components are reasonable if outcomes are measured.

## RESEARCH GAPS AND FUTURE DIRECTIONS

Six gaps stand out. First, trials should report the consensus five-biomarker index alongside any study-specific markers so that results can be compared and pooled, and should add diurnal cortisol slope and HRV to show whether effects extend beyond cardiometabolic markers.<sup>14</sup> Second, trials in healthy, low-AL volunteers are prone to floor effects, so studies should enrol people with elevated baseline AL or high stressor exposure, including disadvantaged groups and under-represented low- and middle-income countries.<sup>89</sup>

Third, no minimal clinically important difference for AL has been defined, and long-term follow-up linking AL change to clinical events is needed before AL can serve as a surrogate. Fourth, mediation analyses should test whether changes in appraisal, sleep or behaviour explain changes in AL, using the stage-based framework to generate hypotheses. Fifth, yoga-based and naturopathic programmes, widely used in India, need adequately powered, pre-registered RCTs with active controls, standardised protocols and both AL and clinical endpoints. Sixth, optimal dose, adherence and durability of effects remain largely unknown.

## Limitations

As a narrative review, this article is susceptible to selection bias; studies were not screened systematically, and trials not indexed in PubMed or not in English may have been missed. Effect sizes were taken from published meta-analyses without re-analysis or formal certainty grading, and many of the underlying trials had high or unclear risk of bias. The intervention framework is proposed as an organising tool and has not been empirically validated. The consensus AL index is recent, so the evidence map relies largely on trials of individual components.

## CONCLUSION

Chronic stress is associated with cardiovascular, metabolic, immune-mediated, gastrointestinal and depressive disorders through interacting neuroendocrine, autonomic, inflammatory and metabolic pathways. AL provides a useful, although imperfect, framework for summarising the cumulative physiological burden associated with repeated or sustained adaptation. Lifestyle interventions can improve individual AL-related biomarkers, with comparatively broad evidence for physical activity and Mediterranean-style dietary patterns, and evidence for benefits from yoga and meditation across selected outcomes. However, evidence that these interventions reduce composite AL, or that such reductions prevent disease, remains limited. Mapping interventions against standardised AL components and clinical endpoints helps distinguish well-supported findings from preliminary evidence and important research gaps. Future rigorous trials using standardised AL measures and clinically meaningful outcomes are needed to determine whether AL can serve as a useful therapeutic target.

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## REFERENCES

- World Health Organization. Stress: questions and answers, 2026. Available at: <https://www.who.int/news-room/questions-and-answers/item/stress>. Accessed on 23 October 2026.
- Selye H. A syndrome produced by diverse nocuous agents. *Nature*. 1936;138:32.
- Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol*. 2009;5(7):374-81.
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338(3):171-9.
- Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA*. 2007;298(14):1685-7.
- Kivimäki M, Nyberg ST, Batty GD, Fransson EI, Heikkilä K, Alfredsson L, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet*. 2012;380(9852):1491-7.
- Hackett RA, Steptoe A. Type 2 diabetes mellitus and psychological stress-a modifiable risk factor. *Nat Rev Endocrinol*. 2017;13(9):547-60.
- Song H, Fang F, Tomasson G, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, et al. Association of stress-related disorders with subsequent autoimmune disease. *JAMA*. 2018;319(23):2388-400.
- McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med*. 1993;153(18):2093-101.
- Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation-allostatic load and its health consequences. *MacArthur studies of successful aging*. *Arch Intern Med*. 1997;157(19):2259-68.
- Guidi J, Lucente M, Sonino N, Fava GA. Allostatic load and its impact on health: a systematic review. *Psychother Psychosom*. 2021;90(1):11-27.
- Parker HW, Abreu AM, Sullivan MC, Vadiveloo MK. Allostatic load and mortality: a systematic review and meta-analysis. *Am J Prev Med*. 2022;63(1):131-40.
- Rosemberg MS, Granner J, Li Y, Seng JS. A scoping review of interventions targeting allostatic load. *Stress*. 2020;23(5):519-28.
- McCorry C, McLoughlin S, Layte R, NiCheallaigh C, O'Halloran AM, Barros H, et al. Towards a consensus definition of allostatic load: a multi-cohort, multi-system, multi-biomarker individual participant data (IPD) meta-analysis. *Psychoneuroendocrinology*. 2023;153:106117.
- Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev*. 2019;4:5.
- Lazarus RS, Folkman S. Stress, appraisal, and coping. New York, NY: Springer; 1984.
- Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res*. 2014;58(2-3):193-210.
- Mattson MP. Hormesis defined. *Ageing Res Rev*. 2008;7(1):1-7.
- Shonkoff JP, Garner AS. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129(1):e232-46.
- Russell G, Lightman S. The human stress response. *Nat Rev Endocrinol*. 2019;15(9):525-34.
- Cadegiani FA, Kater CE. Adrenal fatigue does not exist: a systematic review. *BMC Endocr Disord*. 2016;16(1):48.
- Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci*. 2009;10(6):397-409.
- McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 2007;87(3):873-904.
- Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. *Nat Rev Neurosci*. 2009;10(6):410-22.
- Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review

- of the literature. *Psychiatry Investig.* 2018;15(3):235-45.
26. Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, Gilbert KE. Diurnal cortisol slopes and mental and physical health outcomes: a systematic review and meta-analysis. *Psychoneuroendocrinology.* 2017;83:25-41.
27. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol.* 2002;21(6):531-41.
28. Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci U S A.* 2012;109(16):5995-9.
29. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull.* 2004;130(4):601-30.
30. Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, Zaltsman A, et al. Chronic variable stress activates hematopoietic stem cells. *Nat Med.* 2014;20(7):754-8.
31. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet.* 2017;389(10071):834-45.
32. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet.* 1999;354(9188):1435-9.
33. Siew RVK, Nabe-Nielsen K, Turner AI, Bujtor M, Torres SJ. The role of combined modifiable lifestyle behaviors in the association between exposure to stressors and allostatic load: a systematic review of observational studies. *Psychoneuroendocrinology.* 2022;138:105668.
34. Vanuytsel T, van Wanrooy S, Vanheel H, Vanormelingen C, Verschuere S, Houben E, et al. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. *Gut.* 2014;63(8):1293-9.
35. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. *Physiol Rev.* 2019;99(4):1877-2013.
36. Labanski A, Langhorst J, Engler H, Elsenbruch S. Stress and the brain-gut axis in functional and chronic-inflammatory gastrointestinal diseases: a transdisciplinary challenge. *Psychoneuroendocrinology.* 2020;111:104501.
37. Picard M, McEwen BS. Psychological stress and mitochondria: a systematic review. *Psychosom Med.* 2018;80(2):141-53.
38. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, et al. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A.* 2004;101(49):17312-5.
39. Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, et al. Perceived stress and telomere length: a systematic review, meta-analysis, and methodologic considerations for advancing the field. *Brain Behav Immun.* 2016;54:158-69.
40. Van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, et al. Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. *Neurosci Biobehav Rev.* 2020;117:26-64.
41. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med.* 1998;14(4):245-58.
42. Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health.* 2017;2(8):e356-66.
43. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic programming by maternal behavior. *Nat Neurosci.* 2004;7(8):847-54.
44. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci.* 2009;12(3):342-8.
45. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci.* 2013;16(1):33-41.
46. Zannas AS, Arloth J, Carrillo-Roa T, Iurato S, Röh S, Ressler KJ, et al. Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling. *Genome Biol.* 2015;16:266.
47. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):953-62.
48. Song H, Fang F, Arnberg FK, Mataix-Cols D, Fernández de la Cruz L, Almqvist C, et al. Stress related disorders and risk of cardiovascular disease: population based, sibling controlled cohort study. *BMJ.* 2019;365:l1255.
49. Steptoe A, Kivimäki M. Stress and cardiovascular disease: an update on current knowledge. *Annu Rev Public Health.* 2013;34:337-54.
50. Kivimäki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol.* 2018;15(4):215-29.
51. Yang Z, Zhang J, Qu Z, Zhao Z, Zheng Y. Allostatic load elevates the risk and adverse prognosis of immune-mediated inflammatory diseases: modulatory effects of lifestyle interventions and genetic susceptibility. *J Nutr Health Aging.* 2026;30(3):100792.

52. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry.* 1999;156(6):837-41.
53. Hammen C. Stress and depression. *Annu Rev Clin Psychol.* 2005;1:293-319.
54. Russo SJ, Murrough JW, Han MH, Charney DS, Nestler EJ. Neurobiology of resilience. *Nat Neurosci.* 2012;15(11):1475-84.
55. Goyal M, Singh S, Sibinga EM, Gould NF, Rowland-Seymour A, Sharma R, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern Med.* 2014;174(3):357-68.
56. Pascoe MC, Thompson DR, Jenkins ZM, Ski CF. Mindfulness mediates the physiological markers of stress: systematic review and meta-analysis. *J Psychiatr Res.* 2017;95:156-78.
57. Black DS, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. *Ann N Y Acad Sci.* 2016;1373(1):13-24.
58. Pascoe MC, Thompson DR, Ski CF. Yoga, mindfulness-based stress reduction and stress-related physiological measures: a meta-analysis. *Psychoneuroendocrinology.* 2017;86:152-68.
59. Cramer H, Lauche R, Haller H, Steckhan N, Michalsen A, Dobos G. Effects of yoga on cardiovascular disease risk factors: a systematic review and meta-analysis. *Int J Cardiol.* 2014;173(2):170-83.
60. Cramer H, Ward L, Saper R, Fishbein D, Dobos G, Lauche R. The safety of yoga: a systematic review and meta-analysis of randomized controlled trials. *Am J Epidemiol.* 2015;182(4):281-93.
61. Fincham GW, Strauss C, Montero-Marin J, Cavanagh K. Effect of breathwork on stress and mental health: a meta-analysis of randomised-controlled trials. *Sci Rep.* 2023;13(1):432.
62. Laborde S, Allen MS, Borges U, Dosseville F, Hosang TJ, Iskra M, et al. Effects of voluntary slow breathing on heart rate and heart rate variability: a systematic review and a meta-analysis. *Neurosci Biobehav Rev.* 2022;138:104711.
63. Singh B, Olds T, Curtis R, Dumuid D, Virgara R, Watson A, et al. Effectiveness of physical activity interventions for improving depression, anxiety and distress: an overview of systematic reviews. *Br J Sports Med.* 2023;57(18):1203-9.
64. Noetel M, Sanders T, Gallardo-Gómez D, Taylor P, Del Pozo Cruz B, van den Hoek D, et al. Effect of exercise for depression: systematic review and network meta-analysis of randomised controlled trials. *BMJ.* 2024;384:e075847.
65. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med.* 2017;51(8):670-6.
66. Reimers AK, Knapp G, Reimers CD. Effects of exercise on the resting heart rate: a systematic review and meta-analysis of interventional studies. *J Clin Med.* 2018;7(12):503.
67. Kodama S, Tanaka S, Saito K, Shu M, Sone Y, Onitake F, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Arch Intern Med.* 2007;167(10):999-1008.
68. Umpierre D, Ribeiro PA, Kramer CK, Leitão CB, Zucatti AT, Azevedo MJ, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA.* 2011;305(17):1790-9.
69. Adams-Campbell LL, Taylor T, Hicks J, Lu J, Dash C. The effect of a 6-month exercise intervention trial on allostatic load in Black women at increased risk for breast cancer: the FIERCE study. *J Racial Ethn Health Disparities.* 2022;9(5):2063-9.
70. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med.* 2020;54(24):1451-62.
71. Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, et al. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep.* 2015;38(6):843-4.
72. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry.* 2016;80(1):40-52.
73. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunningham D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med.* 2015;163(3):191-204.
74. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Breen EC, Witarama T, et al. Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. *Sleep.* 2014;37(9):1543-52.
75. Firth J, Marx W, Dash S, Carney R, Teasdale SB, Solmi M, et al. The effects of dietary improvement on symptoms of depression and anxiety: a meta-analysis of randomized controlled trials. *Psychosom Med.* 2019;81(3):265-80.
76. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med.* 2017;15(1):23.
77. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis.* 2014;24(9):929-39.
78. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular

- disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med.* 2018;378(25):e34.
79. Liu RT, Walsh RFL, Sheehan AE. Prebiotics and probiotics for depression and anxiety: a systematic review and meta-analysis of controlled clinical trials. *Neurosci Biobehav Rev.* 2019;102:13-23.
  80. Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. *Gut.* 2020;69(8):1441-51.
  81. Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS Med.* 2010;7(7):e1000316.
  82. Shields GS, Spahr CM, Slavich GM. Psychosocial interventions and immune system function: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry.* 2020;77(10):1031-43.
  83. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svärdsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). *Arch Intern Med.* 2011;171(2):134-40.
  84. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, et al. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev.* 2017;4(4):CD002902.
  85. Moyer CA, Seefeldt L, Mann ES, Jackley LM. Does massage therapy reduce cortisol? A comprehensive quantitative review. *J Bodyw Mov Ther.* 2011;15(1):3-14.
  86. Antonelli M, Barbieri G, Donelli D. Effects of forest bathing (shinrin-yoku) on levels of cortisol as a stress biomarker: a systematic review and meta-analysis. *Int J Biometeorol.* 2019;63(8):1117-34.
  87. Tan M, Mamun A, Kitzman H, Dodgen L. Longitudinal changes in allostatic load during a randomized church-based, lifestyle intervention in African American women. *Ethn Dis.* 2019;29(2):297-308.
  88. Obeng-Nyarko CN, Ralston PA, Wickrama KKAS, Lemacks JL, Ilich JZ. Health for Hearts United longitudinal trial: improving perceived stress and allostatic load outcomes of mid-life and older African American women. *Health Educ Behav.* 2024;51(6):843-52.
  89. Denninger JW, Joss D, Romero PM, Khalsa SBS, Hoge EA, Bhasin M, et al. Psychological assessments, allostatic load and gene expression analyses in a randomized controlled trial comparing meditation, yoga, and stress education. *Front Psychol.* 2025;16:1653242.
  90. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med.* 1996;125(7):605-13.

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