Pharmacomoles

Open Access

Review Article

Relationship between physical inactivity and inflammatory biomarkers (IL-6, TNFα, CRP)

Ahmad Imran Bin Mohd Rosli [1], Muhammad Hazid Najmi Bin Mohd Azemi [1], Muhammad Hafiz Bin Sabri [1*], Mohamad Adam Daniel Bin Mohamad Isa [1]

1 Faculty of Pharmacy, Universiti Sultan Zainal Abidin, Besut, Terengganu, Malaysia

***Corresponding author:** 076819@putra.unisza.edu.my

Citation:
Sabri M H B, Rosli A I B M, Azemi M H N B M, Isa M A D B M. (2026). Relationship between physical inactivity and inflammatory biomarkers (IL-6 TNFα, CRP). *Pharmacomoles,1(1)85-106*

Abstract:

Physical inactivity and sedentary lifestyle contribute to the major causes of diseases and mortality across the world. They are associated closely with low-grade systemic inflammation. This review extracts findings from 56 articles, which includes cross-sectional analyses, prospective cohorts, randomized controlled trials, and systematic reviews, which all evaluate on how physical inactivity and sedentary lifestyle affect key inflammatory biomarkers, which are interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and CRP. The direction and magnitude of these key biomarkers affected by population variables, such as obesity, diabetes, PCOS, cancer survivorship, HIV, multiple sclerosis, and COVID-19 infection. Variation of methodology among researchers, such as biomarker assays, adiposity adjustment and intervention contributed to the inconsistent results. Overall, data shows that low volume of physical activity closely related to increase in inflammation, while exercise has positive anti- inflammatory benefits in variety of the populations.

Keywords: Adiposity; Biomarkers; C-Reactive Protein; Exercise; Health Status; Inflammation; Interleukin-6; Mortality; Sedentary Behavior; Tumor Necrosis Factor-alpha.

Received: 17-12-2025

Revised: 14-04-2026

Accepted: 09-06-2026

Published: 30-06-2026

Introduction

Physical inactivity, recognised by the World Health Organization (WHO) as a major global health concern, is defined as the failure to achieve recommended levels of energy-expending physical movement, while sedentary behaviour refers to any waking activity performed in a sitting, reclining, or lying posture with an energy expenditure of ≤1.5 metabolic equivalents [1,2]. These two behaviours, although related, represent distinct but often co-occurring dimensions of suboptimal lifestyle patterns [3]. Modern environments characterised by prolonged screen exposure, desk-based occupations, and urbanised living have substantially reduced opportunities for regular movement, contributing to persistently high levels of inactivity across all age groups. Current global data show that about one in four adults and more than 80% of teens do not follow the recommended activity guidelines [1,2]. Older adults are also affected because they are less active and spend a lot of time sitting [4]. This prevalent inactivity is linked to considerable public health consequences: the WHO identifies physical inactivity as the fourth principal risk factor for global mortality, responsible for around 6% of deaths globally [5]. Evidence indicates that inadequate physical activity leads to increased adiposity, low-grade systemic inflammation, and an elevated risk for various non- communicable diseases, including cardiometabolic disorders, neurodegenerative conditions, and generalized immune dysfunction [5,6].
Inflammation is a fundamental, evolutionarily conserved host response to tissue insult or infection that manifests as a coordinated sequence of vascular, cellular, and molecular events intended to isolate and eliminate the inciting stimulus and to initiate tissue repair [7]. Rapid and self-limiting inflammation is described as acute inflammation, whereas chronic inflammation denotes a persistent, dysregulated state of immune activation with ongoing

cytokine production and progressive tissue remodelling or damage [8,9]. Contemporary work emphasises that the reach of inflammatory mechanisms extends well beyond classical foci of infection or injury and includes low-grade, sterile forms of metabolic inflammation (often termed "metainflammation") that arise when initiating stimuli persist or resolution mechanisms fail [7,10]. Subclinical, chronic inflammation is increasingly considered a key mechanistic link between adverse lifestyle exposures like physical inactivity, excess adiposity, prolonged sedentary behavior, and a wide range of non-communicable diseases, including cardiometabolic disorders, neurodegeneration, and cancer. This inflammatory burden is quantified using biomarkers from different host response tiers. Researchers observed that cytokines such as IL-6 and TNF-α involved in active immune signalling, while hepatic acute- phase proteins such as CRP is abundant in systemic inflammatory output and are commonly used in clinical and epidemiological studies [9,10]. These measurements show how severe or persistent the inflammation is, helping researchers understand how lifestyle behaviours influence disease risk [7,11].

IL-6, TNF-α, and CRP are inflammatory biomarkers commonly used in lifestyle and epidemiological research because they help differentiate various aspects of the body's inflammatory response[10]. IL-6 is a pleiotropic cytokine that has both pro- and anti-inflammatory actions. It also regulates key metabolic processes such as insulin sensitivity, lipolysis, hepatic acute-phase signalling, and energy expenditure [12]. TNF-α is a powerful upstream mediator of systemic inflammation that activates the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Mitogen-Activated Protein Kinase (MAPK) pathways. This causes the production of cytokines, insulin resistance, and several chronic inflammatory disorders [13,14]. CRP is an acute-phase hepatic protein produced by IL-6. It is an easily measured marker of mild systemic inflammation and is widely used as a predictor of cardiometabolic health [15–17]. IL-6 and TNF-α show cytokine-level activity, while CRP reflects overall inflammation, and together these biomarkers show how lifestyle factors such as physical inactivity, prolonged sitting, and higher body fat contribute to inflammation and increase the risk of non-communicable diseases [9,10].

Previous research had studied the relationship between physical inactivity and sedentary behaviour with increased inflammatory biomarkers. However, there are some contradicting findings. One study reported that higher sedentary time and lower physical activity were linked to increased levels of CRP, leptin, IL-6, and glycoprotein acetyls in children [18]. However, these associations were mostly explained by body fat percentage, and the study found no significant link between screen time and inflammatory biomarkers. Another study, however, reported that physical activity interventions led to a modest reduction in IL-6 levels among individuals with prediabetes. However, they did not significantly affect CRP or TNF-α levels [19]. Conversely, a newer study established that IL-6 and TNF-α levels were influenced not only by physical inactivity but also by dietary practices, adiposity classification, and lifestyle variables. They observed that elevated levels of IL-6 were associated with increased physical activity, suggesting that the body is responding to exercise rather than remaining sedentary [20]. Endurance training lowered levels of CRP, IL-6, and TNF-α; however, these changes were tightly linked to reductions in fat mass. This suggests that exercise-related reductions in inflammation were more consistent among individuals who are overweight and obese [6]. According to another study, there was a notable decrease in CRP levels following exercise, especially in women over 30 [21]. There was also research demonstrated that TNF-α levels were up in sedentary individuals, whereas body fat levels were also increased in this population [22]. This corroborates the notion that inactivity is associated with inflammation.

Despite growing evidence showing physical inactivity causes elevated inflammatory biomarkers, several gaps remain unanswered. Previous studies have shown considerable variability due to differences in participant characteristics, measurement methods, and whether inflammation was assessed independently of adiposity, which often acts as a confounding mediator. Most existing studies focus on exercise interventions, leaving the direct effects of physical inactivity and sedentary behaviour on IL-6, TNF-α, and CRP less well understood, particularly across different age groups and health conditions. In addition, most previous reviews examine these biomarkers individually rather than together, limiting our understanding of how they interact within the broader inflammatory pathway.

Conflicting results, such as the inconsistent effects of inactivity on CRP [6,19] or unexpected positive associations between sports participation and IL-6 [20], highlight methodological limitations and underscore the need for a comprehensive synthesis. Therefore, this review combines results from multiple studies and focuses specifically on the relationship between physical inactivity and IL-6, TNF- α, and CRP biomarkers.

Methodology

This literature review was developed to synthesise the findings from a collection of 36 articles. The methodologies of the included studies were categorised into six main groups; Systematic reviews and meta-analysis, prospective cohort studies, experimental and quasi-experimental trials, cross-sectional studies, secondary analysis and meta-regression, and narrative reviews.

Systematic reviews and Meta-Analysis

This review included several systematic reviews and meta-analysis. One study synthesised twenty-seven articles, including both randomised and non-controlled studies, that tested an exercise-only intervention without a diet program on physically inactive, overweight, or obese adults aged between eighteen to sixty five. The quality of studies were justified using the Physiotherapy Evidence Database (PEDro) scale and the researchers performed a qualitative synthesis [6].

Other reviews conducted full meta-analysis. One review on prediabetes selected nine high-quality Randomized Controlled Trials (RCTs), used the Cochrane Risk of Bias tool for quality assessment, and pooled data using a random-effects model to calculate a pooled Mean Difference (MD) to estimate the average effect while also using I^2 statistic to measure the heterogeneity [19]. A similar review on women with polycystic ovary syndrome (PCOS) included 10 randomized trials, used Cochrane criteria for quality assessment, and also applied a random-effects model to pool the Weighted Mean Difference (WMD), supplemented by I^2 tests for heterogeneity, performed subgroup analyses on the C-reactive protein (CPR) results, and Egger's test for publication bias [21].

Further meta-analyses evaluated exercise in overweight children, with 27 RCTs [25], combined exercise in sedentary adults, with 24 RCTs [33, 50], and calorie restriction with exercise in overweight adults of 23 trials [52]. These studies calculated pooled effect sizes using the Standardized Mean Difference (SMD), assessed heterogeneity using the I^2 and Q statistics, and applied random-effects models [25, 33, 50, 52]. They also employed meta-regressions and subgroup analyses to explore sources of heterogeneity [33, 50, 52].

Prospective Studies

Two prospective studies were included. The first study used data from 4,607 participants in the United Kingdom National Child Development (UKNCD) study to assess sedentary behavior and incident depression. It used Cox proportional hazards regression models to determine risk and a counterfactual mediation analysis to assess the role of CRP [39]. The second study followed 3,143 Finnish adults from the Health 2000 and 2011 surveys. Its primary statistical method was multinomial logistic regression to test the association between baseline high- sensitivity C-reactive protein (hs-CRP) levels and subsequent weight change [40].

Experimental and interventional studies

Two studies used experimental or quasi-experimental designs. One compared 22 sedentary older men against 17 masters athletes over a 12-week, three-phase training intervention. It used a 2x3 mixed-factorial analysis of variance (ANOVA) to check for group and time

interactions on interleukin-6 (IL-6) and hs-CRP, followed by t-tests and analysis of covariances (ANCOVAs) to control for body fat [42]. The other study used a semi-quasi experimental pre- and post-test design, randomizing 27 Coronavirus Disease 2019 (COVID-19) survivors into a training or control group for 8 weeks. It analyzed changes in IL-6 using a mixed-model repeated-measures ANOVA [45].

Cross-sectional studies

The majority of the included studies were cross-sectional studies. Several studies combined objective and self-reported data. One study investigated 390 Finnish children aged between six to eight years old measuring their activity time, heart rate, diet quality, and body fat percentage. Fasting blood samples were taken to measure the levels of inflammation biomarkers such as hs-CRP, leptin, and IL-6 and used linear regression to find correlation [18]. Another analysed 1,622 older adults using combined heart rate and movement sensors for five days. Fasting blood samples were collected to measure inflammatory markers such as CRP and IL-6, endothelial markers tissue plasminogen activator (t-PA) and E-selectin, and adipokines such as leptin and adiponectin. The study employed linear regression and structural equation modeling for mediation [26]. A study of 2,363 adults used activPAL accelerometers, analyzing associations with inflammatory z-scores using multivariable linear regression [37] and another studied on 72 males by using dual-energy x-ray absorptiometry and bioelectrical impedance (DXA/BIA) and applied Structural Equation Modeling (SEM) [49].

Several studies utilised the National Health and Nutrition Examination Survey (NHANES) dataset. These studies typically used weighted multivariable logistic or linear regression to account for the complex sampling design [24, 35, 36, 38, 43]. Mediation analysis was a common technique used to determine if inflammatory markers statistically explained relationships between activity and outcomes like sleep disturbance [43], metabolic dysfunction-associated steatotic liver disease (MASLD) [24], chronic kidney disease [36], or stroke [38]. Next, there were studies which focused on specific populations. Three of the studies focused on obese or diabetic patients. One study of 84 obese adults used multiplex magnetic bead assays for IL-6 and TNF-α and bioelectrical impedance analysis (BIA) for body fat, using non- parametric Mann-Whitney U and Spearman tests [20]. Two studies on 44 postmenopausal women with type-2 diabetes mellitus (T2DM) used the Godin Leisure-Time Exercise Questionnaire (GLTEQ) and Enzyme-Linked Immunosorbent Assay (ELISA) for IL-6, analyzing data with ANCOVA and partial correlations [30, 41].

Other three studies analysed athletes or physically active participants against inactive participants. One study compared 44 runners and 21 controls, taking blood pre- and post-marathon for levels of IL-6 by ELISA and conducting in vitro experiments, analyzed using t-tests and ANOVA [23]. A small study of 12 older men used Wilcoxon Mann-Whitney U tests due to the small sample size [29]. Another study of 33 participants in three activity groups used flow cytometry and ex vivo cultures, analyzed with one-way ANOVA and mixed-effects models [48].

On the other hand, other studies focused on health conditions. One study included 101 elderly people living with Human Immunodeficiency Virus (HIV) where the methodology involved a single baseline visit where the participants self-reported their physical activity and sitting time using International Physical Activity Questionnaire (IPAQ), their blood samples collected for inflammatory biomarkers such as IL-6, CRP and TNF-α, while data for blood pressure and body mass index (BMI) were extracted from clinical records [28]. The researchers used Spearman's Rank Correlation Coefficient for correlations. A study of 108 participants with Type 1 diabetes quantified TNF-α gene expression by using quantitative reverse transcription polymerase chain reaction (qRT-PCR), analyzed with Chi-square test and ANOVA [27].In addition, other studies analysed generally healthy or mixed populations. Two studies recruiting 244 healthy adults used BIA, questionnaires, and ELISA for detection of levels of IL-6, TNF-α, CRP, analyzed with Pearson correlation and multiple linear regression [22, 31]. Another study of 368 biobank participants used ANOVA/Kruskal-Wallis, Spearman's correlation, and multiple linear regression [32].

Secondary analysis and Meta-Regression

This review also included studies conducting secondary mediation analysis based on prior systematic reviews. These analyses selected RCTs from previous reviews, for example, 16 RCTs with female breast cancer survivors. The statistical method involved running a three-level mixed-effects meta-analysis to find the overall effect SMD and then using random-effect meta-regression models to test if changes in body composition mediated the changes in inflammatory markers [34, 51].

Narrative reviews

Finally, two articles were narrative reviews. These papers summarized and synthesized existing literature on IL-6 signaling [46] and the general effect of exercise on cytokines [47]. As they did not conduct new experiments, they did not have a primary statistical analysis section but instead reported the findings from the literature they surveyed.

Discussion

Overview of the articles

In this review we had found 36 articles from multiple sources that are related to the topic. Table 1 below explains about the participants, result, and the statistical methods used by the studies. Increase or decrease of biomarkers in Table 1 shows increase or decrease of biomarkers plasma concentration from their normal level. High level of inflammatory biomarkers may be a sign of inflammation.

Table 1: Summary of Included Studies Examining the Effects of Sedentary Time and Physical Activity on Inflammatory Biomarkers (IL-6, TNF-α, and CRP)

No.	Study by and study type	Participants characterisitics or inclusion/ exclusion criteria	Measured biomarkers as sedentary time increases or as exercising time increase (IL-6, TNF- α, CRP)	Statistical methods used	Comment
1	Haapala et al., (2021). Observational cross-sectional study [18]	390 children (192 girls, 198 boys), aged 6–8 years.	Sedentary time increase: - IL-6 increases, (β = 0.105, 95% CI = 0.005 to 0.205). - CRP increases, (β = 0.170, 95% CI = 0.070 to 0.269)	- Multiple linear regression analyses - Regression models adjusted for covariates (include body fats percentage) - Stratified (interaction) analyses by body fat percentage	- TNF- α are measured but not reported
2	Jadhav et al. (2020). Systematic review and meta-analysis of RCT [19]	1,906 prediabetes patients (9 trials), age 20–70 years	Exercising time increase - IL-6 decrease (MD = -0.15 pg/mL, 95% CI = -0.25 to -0.04) - TNF-α no significant (MD = 0.67 pg/mL, 95% CI = –2.56 to 3.89) - CRP no significant (MD = –0.05 mg/L, 95% CI = –0.33 to 0.23)	- Software used: Review Manager (RevMan) 5.3. - generic inverse variance method: MD, CI, and I^2 reported	
3	Polak- Szczybyło and Tabarkiewicz (2024). Observational cross-sectional study [20]	84 obese adult volunteers, Aged 18 to 73 years. Excluded: pregnant women; people with epilepsy; people with pacemakers, implants or prostheses; those taking drugs	Exercising time increase - IL-6 increase (p = 0.049)	- Software used: Statistica 13.1 - Spearman's rank correlation coefficient Mann– Whitney U test	

		affecting the immune system (steroids, anti- inflammatory drugs, statins); people with cancer or chronic inflammatory diseases; incomplete questionnaire or food diary data.			
4	Gonzalo- Encabo et al. (2021). Systematic review [6]	Overweight or obese adults, physically inactive, participated in an exercise training program (42 studies). age 18-65 years. Excluded: populations with diagnosed cardio-metabolic, immunological, or musculoskeletal pathology	Exercising time increase - IL-6: decrease - TNF-α: decrease - CRP: decrease	-. Only data extraction of pre- vs post- intervention (exercise) differences in cytokine concentrations	- Total participants not specified - Did not report p-values, β coefficients , or confidence intervals
5	Moori et al. (2023) Systematic Review and Meta-Analysis of Randomized Trials [21]	women diagnosed with Polycystic Ovary Syndrome (PCOS) in randomized trials of exercise vs control (10 trials).	Exercising time increase - IL-6: no significant change - TNF-α: no significant change - CRP: decrease, (WMD = –0.43 mg/L, 95% CI = –0.66 to –0.21, P ≤ 0.01)	. - Weighted Mean Difference (WMD) with 95% CI. I^2 statistic	- Total participants not specified - Age of participants not specified - IL-6, and TNF-a, are not included in the meta anlysis due to insufficient studies
6	Silva et al. (2024) Systematic review and meta-analysis of RCT [50]	physically inactive adults, age 18-64 years. Excluded: severe chronic diseases (CVD, cancer, T1/T2 diabetes, liver/kidney disease), aquatic exercise, combined diet + exercise etc.	Exercising time increase - IL-6: no significant, SMD: – 0.877 (95% CI –1.273 to –0.482) p = 0.000 - TNF-α: decrease, SMD: – 0.972, 95% CI [–1.361,	- I^2 statistic. Meta- regression models by age, sex, and intervention length	- IL-6 appears significant decrease for some outcome; but abstract states no significant effect for IL-6.

			–0.582], p < 0.001 - CRP: decrease, SMD: – 0.507, 95% CI [–0.818, –0.196], p = 0.001		
7	Rodas et al. (2020) Observational cross-sectional study [22]	244 healthy volunteers (112 men, 132 women), aged 18-55 years. Excluded: smokers; professional/ elite athletes; significant body-weight fluctuations in previous 2 months (±2 kg)	Sedentary time increase - IL-6: increase (p < 0.001) - TNF-α: increase (p < 0.001) CRP: increase (p not specified	- Multiple linear regression analysis	
8	Bettariga et al. (2025) Systematic review and meta-analysis with secondary mediation analysis of RCT. [51]	752 female survivors of breast cancer (16 RCT). Age > 18 years.	Exercising time increase - IL-6: decrease, p = 0.03. - TNF-α: no significant, p = 0.06. - CRP: decrease, exact p- value not reported.	- Random- effects meta-regression models	
9	Liu et al. (2021) Systematic review and meta-analysis. [52]	1,196 overweight and obese adults.	Exercising time increase - IL-6: no significant, SMD = – 0.04, 95% CI = –0.18 to 0.11, P = 0.62 - TNF-α: no significant, SMD = – 0.14, 95% CI = –0.31 to 0.03, P = 0.11. - CRP: decrease, SMD = – 0.16, 95% CI = –0.29 to –0.03, P = 0.02.	- I^2 statistic. - Meta- regression using STATA version 12	- Age not specified
10	You et al. (2023) Population- based	-244 healthy adults (118 men,	Sedentary time increase	- - multiple linear regression adjusted for	

	cross-sectional study with mediation analysis. [43]	126 women), aged 20-55 years. Excluded: chronic Inflammatory disease, current smokers, pregnancy, CRP >10 mg/L (possible acute infection), recent major surgery (<6 months	- IL-6: increase, MD +0.42 pg/mL (95% CI 0.18– 0.66), p = 0.001 - TNF-α: no significant, MD = 0.03 pg/mL, 95% CI –0.01– 0.07, p = 0.091 - CRP: increase, MD = 0.9 mg/L, 95% CI 0.4–1.3, p = 0.0005	age, sex, BMI, and total physical activity Pearson correlation for biomarker–sedentary time association. Software: SPSS v27.	
11	Werneck et al. (2023) Prospective cohort study with mediation analysis. [39]	4,607 adults (50.4% women). age 40-55 years	Sedentary time increase - CRP: increase, β = –0.03. 95% CI = – 0.04 to – 0.01	- Weighted multivariable logistic regression	
12	Zhou et al. (2025) Cross-sectional study using population survey data [24]	3,729 overweight and obese adults. Age>18 years	Sedentary time increase - CRP: increase, β = 0.92, p < 0.05	- Weighted multivariable logistic regression - Weighted multivariable linear regression	
13	Santa-Paavola et al. (2022) Prospective cohort study. [40]	3,143 adults. age 30–75 years	Sedentary time increase - CRP: no significant, OR = 0.99, 95% CI = 0.96–1.01	- Multinomial logistic regression analyses - Linear regression analyses	- Sedentary time is measured in relation to weight gain.
14	Villar-Fincheira et al. (2021) Observational cross-sectional study [23]	65 males. Age 18-50 years Exclude: presence of morbidity affecting IL-6 levels	Exercising time increase - IL-6: increase, post-marath on plasma IL-6 elevated	- Two-way ANOVA followed by post hoc Sidak test - t-test Pearson's correlation analysis	- 95% CI is not provided

			compared to pre-race		
15	Haber et al. (2022) Observational cross-sectional study. [27]	108 children and adolescents. Age 1–23 years.	Exercising time increase - TNF-α: decrease, p = 0.011	- Two-way ANOVA	- Exercising time is in relation to level of physical activity
16	Elhakeem et al. (2018) Prospective cohort study [26]	1,622 participants (795 men and 827 women) age 60 to 64 years	Exercising time increase - IL-6: decrease - CRP: decrease,	- Linear regression models	- 95% CI is not reported
17	Jones et al. (2023) Observational cross-sectional study. [28]	101 older adults living with HIV. mean age 55.9 year	Sedentary time increase - IL-6: increase - TNF-α: increase	- Multivariable regression models - Mediation/ associative analysis	- 95% CI is not reported
18	Lee (2021) Systematic review and meta-analysis. [25]	27 randomized controlled trials in overweight and obese children and adolescents.	Exercising time increase - IL-6: decrease, SMD = −0.42, 95% CI = −0.70 to −0.14, p = 0.004 - TNF-α: decrease, SMD = −0.31, 95% CI = −0.58 to −0.05, p = 0.021 - CRP: no significant, SMD = −0.09, 95% CI = −0.33 to 0.15, p = 0.452	- Heterogeneity estimated using the Q-statistic Meta-analysis using SMD	- Not specified total participants - p-values, β-coefficients , or 95% CI are not reported
19	Islam et al. (2024) Observational cross-sectional study. [48]	33 participants, age 18–79 year, multiple younger and older participants	Exercising time increase - IL-6:	- One-way ANOVA followed by Tukey's post-hoc testing	Inflammatory biomarker response higher in older active participant vs

		with different activeness	increase, p < 0.01 - TNF-α: no significant, p > 0.71		younger inactive participant
20	Docherty et al. (2022) Narrative review. [47]	Included: studies on exercise and cytokine responses in humans Narrative review	Exercising time increase - IL-6: increase - TNF-α: no significant,	- N/A (Narrative review, the paper does not perform its own statistical analyses)	
21	Nash et al. (2022) Narrative review [46]	Narrative review	Exercising time increase - IL-6: increase	- N/A (a narrative review)	
22	Hayes et al. (2021) Experimental intervention study with cross-sectional comparison of lifelong exercisers. [42]	22 previously sedentary older men (62 ± 2 years) and 17 lifelong-exercising masters athletes (60 ± 5 years)	Exercising time increase - IL-6: decrease, P = 0.030 - CRP: not significant, P = 0.781,	- Two-way ANOVA followed by post-hoc Sidak test - Student's t-test Pearson's correlation	
23	Devasahayam et al. (2021) Observational study with acute exercise challenge (graded maximal test) in Multiple Sclerosis patients and controls. [44]	14 people with progressive Multiple Sclerosis (MS) and 8 controls	During exercise - IL-6: increase, p = 0.003	- Spearman's rank correlation coefficient Related- samples Wilcoxon signed-rank tests	
24	FitzGerald et al. (2012) Observational cross-sectional study. [49]	71 healthy males, age 18–65 years	Exercising time increase - IL-6: decrease, β = –0.27, p = 0.008	- Model fit indices: chi-square, CFI, IFI, RMSEA - Structural equation modeling (SEM)	
25	Binabaji et al., (2024) Experimental intervention study [45]	27 participants who had recently recovered from COVID-19, age 20–45 years	Exercising time increase - IL-6: no significant.	- Mixed model repeated- measures ANOVA - Shapiro–Wilk test Software: SPSS	
26	Jankord and Jemiolo (2004) Observational	73 healthy older men with varying physical	Exercising time Increase IL-6:	- Structural equation modelling (SEM)	

	cross-sectional study. [29]	activity levels, age 55-65 years	decrease, β = −0.27, p = 0.008,	- chi-square, CFI, IFI, RMSEA	
27	Heidari et al. (2025) Observational cross-sectional study. [41]	44 women with type 2 diabetes, aged 50-75 years	Exercising time increase - IL-6: no significant, p = 0.84	- Correlation analyses - Adjusted Analysis of Covariance (ANCOVA)	
28	Peng and Liu (2024) Cross-sectional study [36]	27,808 participants aged 20-80 years	N/A	- Multivariable logistic regression Mediation model	Biomarkers included only Systemic immune inflammation index (SII), neutrophil-to- lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been validated
29	Sha et al. (2024) Cross-sectional study. [35]	24,614 U.S. adults	N/A	- Weighted multiple logistic regression Smoothing curve analysis	Biomarkers included only Monocyte to HDL-C Ratio (MHR), Systemic Inflammatory Response Index (SIRI) and natural log of Systemic Immune- Inflammation Index (InSII)
30	Bai et al. (2024) Cross-sectional observational study. [38]	3,010 participants, age 60 years and older	Sedentary time increase - CRP: increase, OR = 2.602 (95% CI = 1.557 to 4.348), p = 0.003,	- Weighted multivariable logistic regression Smoothed curve fitting and threshold effects analyses	
31	Vandercappelle n et al. (2022) Cross-sectional observational study. [37]	2,363 participants (51.5% male; 28.3% type 2 diabetes; 15.1% prediabetes). Age 40–75 years	Exercising time increase - IL-6: decrease. β = –0.11, 95% CI = –0.15 to –0.08, p < 0.05	- Linear regression models	

			- CRP: decrease β = –0.07, 95% CI = –0.11 to –0.04, p < 0.05		
32	Almuraikhy et al. (2023) Observational cross-sectional study [32]	368 healthy participants, BMI ≥ 20 kg/m^2 & < 30 kg/m^2, age 20-30 years	Exercising time increase - IL-6: increase p = 0.023 - TNF-α: no significant p = 0.78,	- Linear regression models Spearman correlation analysis	
33	Vázquez- Lorente et al. (2025) Randomised controlled intervention study. [33]	100 untrained young healthy adults. BMI 18.5–35 kg/m^2, age 18–25 years	Exercising time increase - IL-6: no significant - TNF-α: no significant - CRP: increase, Δ = 20.1 %, F = 3.339, p = 0.046	- Repeated- measures ANOVA and ANCOVA Software: SPSS v28.0	- Exercise time here are in relation to the intensity of the exercise
34	Jacobs et al. (2025) Observational cross-sectional population study [31]	1,196 Young adults, normal office BP (<140/90 mmHg), age 20-30 years	With central adiposity (Sedentary time increase): - IL-6: increase, β = 0.35, 95% CI = 0.27–0.43, p < 0.001 - CRP: increase, β = 0.42, 95% CI = 0.34– 0.50, p < 0.001	- ANCOVA Multiple regression	The study are associated with central adiposity, not exercise/ sedentary time.
35	Wang et al. (2023) cross-sectional observational population- based study [34]	1,029 older adults, 59.48% women, age 60–88 years	Sedentary time increase - IL-6: increase β = 0.05–	- Multivariable linear regression models Mediation analysis	

			0.08, 95% CI = 0.02 to 0.07 Exercising time increase - IL-6: decrease β = 0.05–0.08, 95% CI = –0.13 to –0.03	
36	Coughlin et al. (2024) Cross-sectional observational study [30]	78 adults, age 40-60 years.	Sedentary time increase - IL-6: increase, β = 0.24, $p < 0.05$ - TNF-α: increase, β = 0.22, $p < 0.05$	- Multivariable linear regression

In this review, we have included multiple types of studies, including 20 cross-sectional studies, 3 experimental intervention studies, 3 prospective cohort studies, 2 narrative reviews, and 7 systematic reviews and meta-analyses. The degree of evidence of the studies is based on the type of study. Meta-analysis and systematic review have a high level of evidence, narrative reviews have a low to moderate level of evidence, RCT or exercise interventions have a moderate level of evidence, prospective cohort studies have a moderate level of evidence, and cross-sectional studies have a low to moderate level of evidence. According to Table 1, we can see that most of the findings reported on exercising time rather than sedentary time. Some findings did not directly report exercising time or sedentary time, like Vázquez-Lorente et al. (2025), they report the intensity of the exercise rather than exercising time, but we relate the intensity to the exercise time proportionally. 2 studies, Peng and Liu (2024) and Sha et al. (2024), did not describe the required biomarkers, but describe other inflammatory biomarkers like immune inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and Monocyte to HDL-C Ratio (MHR). Furthermore, Sha et al. (2024) also used composite biomarkers, namely Systemic Inflammatory Response Index (SIRI) and natural log of Systemic Immune Inflammation Index (lnSII). 3 studies only include children or adolescents below 18 years, 18 studies include adults ranging from 18 to 80 years old, and 5 studies include only older adults ranging from 60 to 88 years old. In addition, 5 studies include obese or overweight participants (BMI>25.0), 2 studies include athletes, 3 studies include diabetes patients, and these disease patients have 1 study each: polycystic ovary syndrome (PCOS), breast cancer, HIV, multiple sclerosis, and COVID-19. 11 studies report on sedentary time and 23 report on exercising time.

Effects of exercising time or sedentary time against inflammatory biomarkers level (IL-6, TNF- α, and CRP)

7 studies find that plasma IL-6 increases as sedentary time increases at resting state, 6 studies find that IL-6 increases with exercise time, and 11 studies find that IL-6 decreases with exercise time. Commonly, participating in an exercise regimen usually results in lower resting IL-6 levels (Nash et al., 2022). As sedentary time decreases or exercise time increases, IL-6 should be lower at the resting state; however, IL-6 would rise during exercise since it is being released from working muscle fibers. This explains the findings by Almuraikhy et al. (2023), Nash et al. (2022), Docherty et al. (2022), Islam et al. (2024), Villar-Fincheira et al. (2021), and Polak- Szczybyło and Tabarkiewicz (2024). Villar-Fincheira et al. (2021) clearly show in their study that post-marathon plasma IL-6 is higher than pre-marathon. Their study also includes two groups of athletes, one group with a high amount of training and the other group with a lower amount of training. In an athletic person, the concentration of IL-6 may increase as much as 10 to 100-fold after a strenuous and prolonged exercise like a marathon race [53]. The pre- marathon plasma IL-6 for both groups is about the same; however, post-marathon plasma IL- 6 is much higher in the first group. This might be due to the stress on the muscles of the athletes, which had damaged the muscle fibers. The same damage might also occur to a person who is not accustomed to vigorous exercise. The damage causes the macrophages to release IL-6 as a myokine that will promote tissue repair. They use two-way ANOVA followed by post hoc Sidak test, student's t-test, and Pearson's correlation analysis to analyse their result.

3 studies found that TNF-α at rest increases with sedentary time, and 4 studies found that TNF- α decreases when exercise time increases. No studies found that TNF-α decreases when sedentary time increases, nor did any studies find that TNF-α increases with exercise time. Most of the time, a decrease of TNF- α and also IL-6 in an active person is due to the reduction of low-grade systemic inflammation.

7 studies found that CRP increases with sedentary time, and 8 studies found that CRP decreases when exercise time increases. No studies found that CRP decreases when

sedentary time increases, but 1 study found that CRP increases with exercise. Vázquez-Lorente et al. (2025) is the previously mentioned study. They experimented on 100 untrained young healthy adults to do vigorous exercise, and their level of CRP was measured. Since this experiment forces untrained people to do vigorous exercise, the stress causes damage to the muscle fiber that causes the release of IL-6, TNF-α, and other inflammatory markers to promote tissue repair and inflammation. IL-6 will also stimulate the liver to produce CRP into the bloodstream, causing an elevated level of plasma CRP. CRP usually acts as an acute-phase marker of systemic inflammation [54].

Effects of certain diseases on exercising time or sedentary time against inflammatory biomarkers level (Il-6, Tnf- A, And Crp)

Diabetes

From the table we could see that 3 studies included diabetes patient. The studies are by Jadhav et al. (2020), Heidari et al. (2025), and Vandercappellen et al. (2022). Jadhav et al. (2020) reported that diabetes is associated with elevated inflammatory biomarkers due to chronic hyperglycemia and metabolic dysregulation, which promotes systemic low-grade inflammation. Their findings shows that IL-6 decreases as exercising time increases even in patients with diabetes. However, they found that TNF-a and CRP has no significant differences. Heidari et al. (2025) experimented on 44 women with type 2 diabetes and found out that as exercising time increase, IL-6 did not significantly decrease. This might be caused by the already high level of resting IL-6 even at sedentary, even when exercising regularly. In addition, Vandercappellen et al. (2022) reported that IL-6 and CRP decrease when exercise time for the normal participants. However, the study actually compares the level of low-grade inflammation and endothelial dysfunction between normal, prediabetes patients and diabetes patients in a vigorous exercise regimen.For all participants, regression analysis showed a β of –0.11 for low- grade inflammation and β of –0.11 for endothelial dysfunction, indicating that higher total physical activity is associated with lower level of low-grade inflammation and its biomarkers and it also shows that endothelial dysfunction decreased as exercising time increases. Furthermore, through their stratified analysis, we could see that endothelial dysfunction is higher in both prediabetes (β = –0.16) and type 2 diabetes (β = –0.14) groups.

Breast cancer and polyscystic ovary syndrome (PCOS)

Bettariga et al. (2025) had done a systematic review and meta-analysis on 16 articles and managed to obtain a total of 752 female survivors of breast cancer. They found that as total aerobic training time increases, IL-6 decreases, but TNF-α and CRP do not show a significant decrease. They stated that the cancer itself and the side effects of cancer treatments may elevate levels of inflammatory biomarkers, which explains the nonsignificant decrease in TNF-α and CRP. They also stated that the reduction of inflammation is very important in cancer patients, as inflammation may promote tumor progression.

Moori et al. (2023) conducted a systematic review and meta-analysis of randomized clinical trials on 10 trials regarding exercise and inflammatory biomarkers in women diagnosed with Polycystic Ovary Syndrome (PCOS). They found that as exercise time increases, IL6 and TNF-α do not decrease significantly, and only CRP decreases significantly. They reported that the exercise group CRPWMD is –0.43 mg/L, meaning that the amount of CRP in the exercise group is 0.43mg/L lower than the non-exercise group (control). Unlike breast cancer, the PCOS tumor is malignant and does not spread like cancer, but it still increases inflammatory biomarkers in certain ways. Insulin resistance is common in PCOS, which may activate inflammatory signalling and cause oxidative stress. In addition, PCOS may cause

hyperandrogenism, which may stimulate immune cell infiltration and inflammatory signalling in ovarian and extra-ovarian tissues [55]. Thus, the reduction of IL6 and TNF-α may not decrease significantly due to those mechanisms.

HIV and COVID-19

Jones et al. (2023) conducted an observational cross-sectional study on 101 older adults living with HIV to measure the inflammatory biomarkers as sedentary time increases. They found out that as sedentary time increases, IL-6 and TNF-α increase. They reported that the average amount of IL-6 is 2.94 pg/mL with a SD of 9.68, and TNF-α is 3.72 pg/mL with a SD of 3.60 in those people, which are slightly higher than the normal amount. However, the rise in inflammatory biomarkers here is probably due to HIV, which promotes chronic immune activation and systemic inflammation. This is due to the white blood cells or macrophages releasing more inflammatory biomarkers to counteract the viral infection. The treatment of HIV may also contribute to the rise of inflammatory biomarkers, they stated.
Binabaji et al. (2024) had initiated an experimental intervention study on 27 participants who had recently recovered from COVID-19 to measure the amount of IL-6 as exercising time increases. They found out that the decrease in IL-6 is not significant as the exercise time increases. They report that after 8 weeks of exercise, serum IL-6 decreased by ~47% but the result is not significant. The reason for this might be the same as that of the previously mentioned HIV patients. The presence of the virus causes the inflammatory markers in the body to elevate. Even though the participants have already recovered from COVID-19, the elevated level of IL-6 may linger for more than one month [56]. The study also stated that participants were only 10 to 30 days after a positive COVID-19 PCR test when they participated in the experiment. The amounts of inflammatory biomarkers at rest in these participants is already elevated, resulting in a higher amount of inflammatory biomarkers even after exercise.

Progressive multiple sclerosis (MS)

Devasahayam et al. (2021) had initiated an observational study with an acute exercise challenge in 14 multiple sclerosis patients and 8 control participants. The study found that IL-6 is higher at resting states for MS patients. The study also shows that patients with high aerobic fitness showed a strong positive association between fitness and the ratio of Brain-Derived Neurotrophic Factor (BDNF) to IL-6, which indicates a shift from a more inflammatory phenotype towards a repair phenotype. The shift means that the body's signaling is more oriented toward tissue repair, growth, and recovery instead of signaling for inflammatory markers. Thus, it is proven that regular exercise is important for MS patients to reduce inflammation and to shift their brain into signaling for repair molecules.

Conclusion

In conclusion, this review compiled many findings that physical inactivity and sedentary lifestyle lead to increase level of inflammatory biomarkers which lead to low-grade systemic inflammation. While acute exercise might momentarily increase IL-6 as part of normal metabolic and tissue-repair signalling, regular physical activity, especially structured exercise training, is generally helpful in decreasing resting inflammatory biomarker levels. The benefits of exercise are noticeable when body fat is reduced. This shows that the role of adiposity as mediator and amplifier of inflammation processes. However, populations with conditions such as diabetes, PCOS, cancer, and COVID-19, show inconsistent biomarkers responses. The overall findings strongly support that when physical activity increases and sedentary time decreases, systemic inflammation decreases, even though there are some

variations between study design and populations characteristics. For more accurate results, future research should focus more on standardise assessment techniques, and a clear distinction between acute and chronic responses.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors received no any financial support for this publication.

References

1. 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. https://doi.org/10.1136/bjsports-2020-102955
2. Chaput JP, Willumsen J, Bull F, Chou R, Ekelund U, Firth J, et al. 2020 WHO guidelines on physical activity and sedentary behaviour for children and adolescents aged 5–17 years: summary of the evidence. *Int J Behav Nutr Phys Act*. 2020;17(1):141. https://doi.org/10.1186/s12966-020-01037-z
3. Pechtl SML, Kim LP, Jacobsen KH. Physical Inactivity and Sedentariness: Languorous Behavior Among Adolescents in 80 Countries. *J Adolesc Health*. 2022;70(6):950–60. https://doi.org/10.1016/j.jadohealth.2021.12.008
4. Gomes ESA, Ramsey KA, Rojer AGM, Reijnierse EM, Maier AB. The association of objectively measured physical activity and sedentary behavior with (Instrumental) activities of daily living in community-dwelling older adults: A systematic review. *Clin Interv Aging*. 2021;16:1877–915. https://doi.org/10.2147/CIA.S325580
5. Ricci F, Izzicupo P, Moscucci F, Sciomer S, Maffei S, Di Baldassarre A, et al. Recommendations for Physical Inactivity and Sedentary Behavior During the Coronavirus Disease (COVID-19) Pandemic. *Front Public Health*. 2020;8:199. https://doi.org/10.3389/fpubh.2020.00199
6. Gonzalo-Encabo P, Maldonado G, Valadés D, Ferragut C, Pérez-López A. The role of exercise training on low-grade systemic inflammation in adults with overweight and obesity: A systematic review. *Int J Environ Res Public Health*. 2021;18(24):13258. https://doi.org/10.3390/ijerph182413258
7. Gusev E, Zhuravleva Y. Inflammation: A New Look at an Old Problem. *Int J Mol Sci*. 2022;23(9):4596. https://doi.org/10.3390/ijms23094596
8. Deng W, Du H, Liu D, Ma Z. Editorial: The Role of Natural Products in Chronic Inflammation. *Front Pharmacol*. 2022;13:1044331. https://doi.org/10.3389/fphar.2022.1044331
9. Menzel A, Samouda H, Dohet F, Loap S, Ellulu MS, Bohn T. Common and novel markers for measuring inflammation and oxidative stress ex vivo in research and clinical practice—which to use regarding disease outcomes? Antioxidants. 2021;10(3):414. https://doi.org/10.3390/antiox10030414
10. van de Vyver M. Immunology of chronic low-grade inflammation: relationship with metabolic function. *J Endocrinol*. 2023;257(2):e220241. https://doi.org/10.1530/JOE-22-0241
11. da Silva BR, Orsso CE, Gonzalez MC, Sicchieri JMF, Mialich MS, Jordao AA, et al. Phase angle and cellular health: inflammation and oxidative damage. *Rev Endocr Metab Disord*. 2023;24(3):543–62. https://doi.org/10.1007/s11154-023-09794-x
12. Hirano T. IL-6 in inflammation, autoimmunity and cancer. *Int Immunol*. 2021;33(12):127–48. https://doi.org/10.1093/intimm/dxab071
13. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, et al. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. *Int J Mol Sci*. 2021;22(5):2719. https://doi.org/10.3390/ijms22052719
14. Rolski F, Błyszczuk P. Complexity of TNF-α signaling in heart disease. *J Clin Med*. 2020;9(10):3267. https://doi.org/10.3390/jcm9103267
15. Pathak A, Agrawal A. Evolution of C-reactive protein. *Front Immunol*. 2019;10:943. https://doi.org/10.3389/fimmu.2019.00943
16. Osimo EF, Baxter LJ, Lewis G, Jones PB, Khandaker GM. Prevalence of low-grade inflammation in depression: A systematic review and meta-analysis of CRP levels. *Psychol Med*. 2019;49(12):1958–70. https://doi.org/10.1017/S003329171900145X
17. Rizo-Téllez SA, Sekheri M, Filep JG. C-reactive protein: a target for therapy to reduce inflammation. *Front Immunol*. 2023;14:1223575. https://doi.org/10.3389/fimmu.2023.1223575
18. Haapala EA, Väistö J, Ihalainen JK, González CT, Leppänen MH, Veijalainen A, et al. Associations

of physical activity, sedentary time, and diet quality with biomarkers of inflammation in children. *Eur J Sport Sci*. 2022;22(6):906–15. https://doi.org/10.1080/17461391.2021.1905078
19. Jadhav RA, Maiya GA, Hombali A, Umakanth S, Shivashankar KN. Effect of physical activity promotion on adiponectin, leptin and other inflammatory markers in prediabetes: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol*. 2021;58(4):419–29. https://doi.org/10.1007/s00592-020-01639-6
20. Polak-Szczybyło E, Tabarkiewicz J. Influence of dietary and lifestyle factors on levels of inflammatory markers (IL-6, IFN-γ and TNF-α) in obese subjects. *Cent Eur J Immunol*. 2024;49(1):19–25. https://doi.org/10.5114/ceji.2024.136894
21. Hafizi Moori M, Nosratabadi S, Yazdi N, Kasraei R, Abbasi Senjedary Z, Hatami R. The Effect of Exercise on Inflammatory Markers in PCOS Women: A Systematic Review and Meta-Analysis of Randomized Trials. *Int J Clin Pract*. 2023;2023:6618526. https://doi.org/10.1155/2023/6618526
22. Rodas L, Riera-Sampol A, Aguilo A, Martínez S, Tauler P. Effects of habitual caffeine intake, physical activity levels, and sedentary behavior on the inflammatory status in a healthypopulation. *Nutrients*. 2020;12(8):2325. https://doi.org/10.3390/nu12082325
23. Villar-Fincheira P, Paredes AJ, Hernández-Díaz T, Norambuena-Soto I, Cancino-Arenas N, Sanhueza-Olivares F, et al. Soluble Interleukin-6 Receptor Regulates Interleukin-6-Dependent Vascular Remodeling in Long-Distance Runners. *Front Physiol*. 2021;12:733150. https://doi.org/10.3389/fphys.2021.733150
24. Zhou Z, Li L, Wang C, Li S, Chen P, Huang J, et al. The association between sedentary behavior and MASLD in overweight and obese adults: investigating the role of inflammatory markers using NHANES data (2017–March 2020). *Front Nutr*. 2025;12:1502341. https://doi.org/10.3389/fnut.2025.1502341
25. Lee J. Influences of exercise interventions on overweight and obesity in children and adolescents. *Public Health Nurs*. 2021;38(3):502–16. https://doi.org/10.1111/phn.12871
26. Elhakeem A, Cooper R, Whincup P, Brage S, Kuh D, Hardy R. Physical activity, sedentary time, and cardiovascular disease biomarkers at age 60 to 64 years. *J Am Heart Assoc*. 2018;7(16):e008250. https://doi.org/10.1161/JAHA.117.008250
27. dos Santos Haber JF, Chagas EFB, Barbalho SM, Sgarbi JA, Haber RSDA, de Labio RW, et al. Level of physical activity and gene expression of IL-10 and TNF-α in children and adolescents with Type 1 diabetes. *J Diabetes Complications*. 2022;36(2):108092. https://doi.org/10.1016/j.jdiacomp.2021.108092
28. Jones R, Enogela EM, Buchanan TL, Buford TW, Vance DE, Fazeli PL. Inflammatory and Cardiovascular Correlates of Physical Activity and Sedentary Behavior in Older Adults Living With HIV. *J Phys Act Health*. 2023;20(2):149–56. https://doi.org/10.1123/jpah.2022-0346
29. Jankord R, Jemiolo B. Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men. *Med Sci Sports Exerc*. 2004;36(6):960–4. https://doi.org/10.1249/01.mss.0000128148.40693.2d
30. Coughlin GH, Antush MT, Vella CA. Associations of sedentary behavior and screen time with biomarkers of inflammation and insulin resistance. *J Behav Med*. 2024;47(5):828–38. https://doi.org/10.1007/s10865-024-00494-1
31. Jacobs A, Kruger R, Smith W, Mokhaneli MC, Mels CMC. Profiling endothelial function, oxidative stress and inflammatory biomarkers in individuals with various cardiovascular risk factors: the African-PREDICT study. *Hypertens Res*. 2025. https://doi.org/10.1038/s41440-024-01822-x
32. Almuraikhy S, Sellami M, Al-Amri HS, Domling A, Althani AA, Elrayess MA. Impact of Moderate Physical Activity on Inflammatory Markers and Telomere Length in Sedentary and Moderately Active Individuals with Varied Insulin Sensitivity. *J Inflamm Res*. 2023;16:5427–38. https://doi.org/10.2147/JIR.S433367
33. Vázquez-Lorente H, Herrera-Quintana L, Acosta FM, Amaro-Gahete FJ, Ruiz JR. Low-grade systemic inflammation biomarkers in sedentary young healthy adults are not significantly affected by a 24-week concurrent training intervention. *Ann N Y Acad Sci*. 2025;1547(1):154–69.

https://doi.org/10.1111/nyas.15288
34. Wang Y, Han Q, Han X, Dong Y, Mao M, Wang C, et al. Objectively-measured movement behaviors, systemic low-grade inflammation, and plasma neurofilament light chain in older adults: a population-based study. *Immun Ageing*. 2023;20(1):68. https://doi.org/10.1186/s12979-023-00392-w
35. Sha S, Bu XP, Wang AW, Chen HZ. Association between inflammatory biomarkers and hypertension among sedentary adults in US: NHANES 2009–2018. *J Clin Hypertens*. 2024;26(8):945–54. https://doi.org/10.1111/jch.14841
36. Peng P, Liu Z. Mediating role of inflammatory biomarkers on the association of physical activity, sedentary behaviour with chronic kidney disease: a cross-sectional study in NHANES 2007–2018. *BMJ Open*. 2024;14(11):e087123. https://doi.org/10.1136/bmjopen-2024-087123
37. Vandercappellen EJ, Koster A, Savelberg HHCM, Eussen SJPM, Dagnelie PC, Schaper NC, et al. Sedentary behaviour and physical activity are associated with biomarkers of endothelial dysfunction and low-grade inflammation-relevance for (pre)diabetes: The Maastricht Study. *Diabetologia*. 2022;65(5):812-823. https://doi.org/10.1007/s00125-022-05651-3
38. Bai L, Wen Z, Yan X, Wu S, Chen J. Association of physical activity, sedentary behavior and stroke in older adults. *Front Public Health*. 2024;12:1359678. https://doi.org/10.3389/fpubh.2024.1359678
39. Werneck AO, Owen N, Araujo RHO, Silva DR, Hallgren M. Mentally-passive sedentary behavior and incident depression: Mediation by inflammatory markers. *J Affect Disord*. 2023;339:847–53. https://doi.org/10.1016/j.jad.2023.07.085
40. Santa-Paavola R, Lehtinen-Jacks S, Jääskeläinen T, Männistö S, Lundqvist A. The association of high-sensitivity C-reactive protein with future weight gain in adults. *Int J Obes*. 2022;46(6):1234–40. https://doi.org/10.1038/s41366-022-01114-1
41. Heidari Z, Molanouri Shamsi M, Kadkhodaei A, Behmanesh M, Shahrbanian S, Soudi S. Interplay between physical activity, inflammation, and cognitive performance in women with type 2 diabetes: an observational study focused on IL-6 pathway mediators. *Diabetol Metab Syndr*. 2025;17(1):12. https://doi.org/10.1186/s13098-024-01521-w
42. Hayes LD, Herbert P, Sculthorpe NF, Grace FM. Short-Term and Lifelong Exercise Training Lowers Inflammatory Mediators in Older Men. *Front Physiol*. 2021;12:719983. https://doi.org/10.3389/fphys.2021.719983
43. You Y, Chen Y, Fang W, Li X, Wang R, Liu J, et al. The association between sedentary behavior, exercise, and sleep disturbance: A mediation analysis of inflammatory biomarkers. *Front Immunol*. 2023;13:1082084. https://doi.org/10.3389/fimmu.2022.1082084
44. Devasahayam AJ, Kelly LP, Williams JB, Moore CS, Ploughman M. Fitness shifts the balance of BDNF and IL-6 from inflammation to repair among people with progressive multiple sclerosis. *Biomolecules*. 2021;11(4):597. https://doi.org/10.3390/biom11040597
45. Binabaji S, Rahimi M, Rajabi H, Keshavarz M, Rahimi R, Ahmadi A, et al. Effects of physical training on coagulation parameters, interleukin-6, and angiotensin-converting enzyme-2 in COVID-19 survivors. *Sci Rep*. 2024;14(1):15234. https://doi.org/10.1038/s41598-024-65981-2
46. Nash D, Hughes MG, Butcher L, Aicheler R, Smith P, Cullen T, et al. IL-6 signaling in acute exercise and chronic training: Potential consequences for health and athletic performance. *Scand J Med Sci Sports*. 2023;33(1):4–19. https://doi.org/10.1111/sms.14231
47. Docherty S, Harley R, McAuley JJ, Crowe LAN, Pedret C, Kirwan PD, et al. The effect of exercise on cytokines: implications for musculoskeletal health: a narrative review. *BMC Sports Sci Med Rehabil*. 2022;14(1):5. https://doi.org/10.1186/s13102-022-00397-2
48. Islam H, Boultbee J, Jackson GS, Mui AL, Little JP. Cross-sectional analysis of blood leukocyte responsiveness to interleukin-10 and interleukin-6 across age and physical activity level. *Transl Exerc Biomed*. 2024;1(3–4):255–63. https://doi.org/10.1016/j.trexb.2024.10.002
49. FitzGerald L, Macey PM, Brecht ML. Pathways to interleukin-6 in healthy males and serious leisure male athletes: Physical activity, body composition and age. *PLoS ONE*.

2012;7(7):e40626. https://doi.org/10.1371/journal.pone.0040626
50. Silva FM, Duarte-Mendes P, Teixeira AM, Soares CM, Ferreira JP. The effects of combined exercise training on glucose metabolism and inflammatory markers in sedentary adults: a systematic review and meta-analysis. *Sci Rep*. 2024;14(1):2105. https://doi.org/10.1038/s41598-024-52643-4
51. Bettariga F, Taaffe DR, Borsati A, Avancini A, Pilotto S, Lazzarini SG, et al. Exercise and inflammation in female survivors of breast cancer: systematic review and meta-analysis with secondary mediation analysis on body composition. *J Cancer Surviv*. 2025. https://doi.org/10.1007/s11764-024-01642-x
52. Liu Y, Hong F, Lebaka VR, Mohammed A, Ji L, Zhang Y, et al. Calorie Restriction With Exercise Intervention Improves Inflammatory Response in Overweight and Obese Adults: A Systematic Review and Meta-Analysis. *Front Physiol*. 2021;12:713670. https://doi.org/10.3389/fphys.2021.713670
53. Pedersen BK, Steensberg A, Schjerling P. Exercise and interleukin-6. *Curr Opin Hematol*. 2001;8(3):137–41. https://doi.org/10.1097/00062752-200105000-00002
54. International Association for the Study of Pain. Low-grade inflammation and the brain [Internet]. Washington (DC): IASP; 2021 Nov 2 [cited 2025 Nov 17]. Available from: https://www.iasp-pain.org/publications/relief-news/article/low-grade-inflammation-brain/
55. Deng H, Chen Y, Xing J, Zhang N, Xu L. Systematic low-grade chronic inflammation and intrinsic mechanisms in polycystic ovary syndrome. *Front Immunol*. 2024;15:1470283. https://doi.org/10.3389/fimmu.2024.1470283
56. Ahmed AS, Mahmoud MA, Gad H, Antar M, Elgazar A, Anil V, et al. Longitudinal analysis of traditional inflammatory markers (IL-6, CRP) juxtaposed with heparin-binding protein (HBP) and serum amyloid A protein component (SAA) during acute infection and convalescence from COVID-19 infection. *J Immunol Res*. 2025;2025:8881752. https://doi.org/10.1155/2025/8881752