



# The Effect of Dietary Glycemic Index on Inflammatory Biomarkers: A Systematic Review with Consideration of Confounders

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ARTICLE INFO	ABSTRACT
<b>Article type:</b> Review Article	<b>Introduction:</b> The glycemic index (GI) and inflammation are associated with several diseases; however, the relationship between GI and inflammation remains unclear. In this systematic review, the authors hypothesize that GI influences inflammatory biomarkers but can be significantly affected by unrecognized statistical confounders.
<b>Article History:</b> Received: 21 Sep 2024 Accepted: 01 Mar 2025	<b>Methods:</b> A comprehensive search was made in ScienceDirect, Web of Science, PubMed, Directory of Open Access Journals (DOAJ), and Google Scholar from 2010 to April 2022 using MESH and un-MESH keywords. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) were used.
<b>Keywords:</b> Glycemic Index Inflammation Biomarkers Carbohydrates	<b>Results:</b> Out of 24,577 studies, 14, including one master's thesis, were included in this review. Seven of these studies were conducted on individuals with a disease, six were on healthy or obese individuals without other illnesses, and one focused on pregnant women. IL-6 was measured in 8 studies, TNF- $\alpha$ in 7, CRP in 6, and hs-CRP in 2. Five well-designed studies confirmed that GI can influence inflammation, while seven found no association. Several unaddressed confounders and limitations were identified across the studies. The primary factors affecting the results were dietary patterns, metabolic factors, and food processing.  <b>Conclusion:</b> Based on the results, evidence supports a slight effect of GI on inflammatory biomarkers. The bias risk in different studies is high. More studies are required, and this review provides essential considerations to lower the bias risks for further studies.

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## Introduction

Inflammation is a protective biological response involving the immune system, tissues, and organs to various harmful stimuli, such as pathogens, cellular damage, and surgery (1-3). Overall, inflammation is a key driver of many diseases (1, 2). Several factors can be used to assess the severity of inflammation, with

inflammatory blood biomarkers being among the most crucial (1, 2, 4).

Recent studies have demonstrated that dietary intake significantly influences pro-inflammatory processes and the severity of chronic diseases (3, 5-8). Notably, strong associations have been found between carbohydrate and sugar consumption, insulin levels, and the risk of inflammation and chronic diseases (9-11).

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The glycemic index (GI), introduced by Jenkins et al. (12) in the 1980s, is a key measure for assessing the quality of carbohydrates. It is defined as the degree and duration of blood glucose elevation following fasting in response to the consumption of a specific carbohydrate, compared to a standard (typically glucose or white bread). The GI is scaled from 0 to 100 and is categorized into Low GI (<56), Medium GI (56-69), and High GI (>69) (12-14).

Recent studies have highlighted an association between dietary GI and various chronic diseases, particularly diabetes, cardiovascular diseases, and breast cancer (9, 10, 15-21). Obesity is another factor that increases the risk of inflammation in individuals, and some studies have also shown a significant association between GI and weight management (22-25). Furthermore, the inflammatory effects of GI and carbohydrate intake have been discussed in systematic reviews and meta-analyses as potential mediators of breast cancer (10). However, a meta-analysis in 2018 found no significant relationship between GI and inflammatory cytokines, including CRP, leptin, IL-6, and TNF- $\alpha$  (26).

Despite some studies indicating a pro-inflammatory effect of Glycemic Load (GL) (9, 10, 26), the overall impact of GI on inflammation remains unclear. GL is a measure that estimates the increase in blood glucose levels after consuming carbohydrates (9, 10, 26). In other words, it is still uncertain whether the quality of carbohydrates contributes to inflammation or if only the quantity plays a role. While GL estimates the blood glucose increase after carbohydrate consumption, it does not fully account for

carbohydrate quality. Previous research suggests that GL is confounded by carbohydrate quantity, making it an inadequate independent measure (13). In contrast, GI is independent of carbohydrate weight, allowing it to more accurately represent carbohydrate quality (12-14).

The conflicting results in the existing literature highlight a significant research gap: while some studies support the role of GI in promoting inflammation, others fail to find a significant correlation between GI and inflammatory cytokines such as CRP, leptin, IL-6, and TNF- $\alpha$  (26). Therefore, this systematic review aims to evaluate the impact of the Glycemic Index on inflammatory biomarkers, specifically IL-6, IL-1, TNF- $\alpha$ , CRP, and hs-CRP, independent of GL. This review seeks to clarify the association between carbohydrate quality and inflammation, identify biases in prior studies, and provide recommendations for future research. The authors hypothesize that GI influences inflammatory biomarkers; however, previous studies have often overlooked significant confounders that must be addressed.

## Materials and Methods

### Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this study. Three independent researchers (PM, PZSh, and AV) searched scientific databases, including ScienceDirect, Web of Science, PubMed, and the Directory of Open Access Journals (DOAJ), covering the period from 2010 to April 2022 (Table 1).

**Table 1.** PICO criteria for inclusion of studies in the systematic review

PICO component	Description
Population	age $\geq$ 18 years old, in any country, with or without a disease
Intervention	With low GI or high GI diet pattern or report the GI score of diet (GL studies excluded)
Comparators	N/A
Outcomes	Reported any changes in IL-6, IL-1, TNF- $\alpha$ , CRP, and HS-CRP
Study design	All original studies on human subjects include: Case-Control Studies, Intervention Studies, Cross-sectional studies, cohort studies
Language	English, Farsi

GI: Glycemic Index, GL: Glycemic Load, IL-6: Interleukin-6, IL-1: Interleukin-1, TNF- $\alpha$ : Tumor Necrosis Factor Alfa, CRP: C-Reactive Protein, HS-CRP: High Sensitive C-Reactive Protein, N/A: Not applied

The search timeline was limited based on two factors: 1) the update to the GI table in 2008 (27) and 2) a comprehensive discussion by Galland et al. (9) followed by Milajerdi et al.'s (26) study in

2010. Additionally, a thorough search was conducted in Google Scholar from 2010 to April 2022, and relevant articles from this database were included in the study.

### Search Keywords

In this systematic review, a comprehensive search strategy was employed, utilizing both Medical Subject Headings (MeSH) and non-MeSH keywords tailored to the search protocols of each database to identify relevant studies on the relationship between the glycemic index and inflammation. The search included keywords such as "Glycemic Index," along with various MeSH terms related to its epidemiology, etiology, immunology, physiology, and more, alongside non-MeSH terms like "glycemic index," "GI," and "glycaemic indices." Inflammation-related terms included both MeSH and non-MeSH keywords such as "inflammation," inflammatory biomarkers, specific interleukins (e.g., IL-1, IL-6, IL-10), tumor necrosis factor (TNF), C-reactive protein (CRP), and other inflammatory indices and mediators. To ensure comprehensiveness, related systematic reviews were consulted, and a secondary search was performed by a fourth researcher using a simplified query of ("glycemic index" OR GI) and "inflammatory biomarkers." The search results from all databases were consolidated, and duplicate articles were removed. Finally, the findings were systematically organized into a single comprehensive file for analysis.

### Inclusion and Exclusion Criteria

All clinical trials, case-control studies, cohort studies, and cross-sectional human studies published from 2010 to April 2022 that examined the effect of diet based on GI (Low/High GI) on inflammatory biomarkers or inflammation were considered. Studies such as duplicates, reviews, systematic reviews, meta-analyses, preprints, open-review manuscripts, editorial letters, conference abstracts, and short communications were excluded. Other exclusion criteria included: 1) studies conducted in children or animals due to biological and physiological differences, 2) studies that did not consider GI as a separate factor from GL, 3) studies that did not report inflammatory biomarkers in measurable values, 4) studies involving interventions other than dietary patterns, including medical, physical activity, exercise, or supplementary interventions, 5)

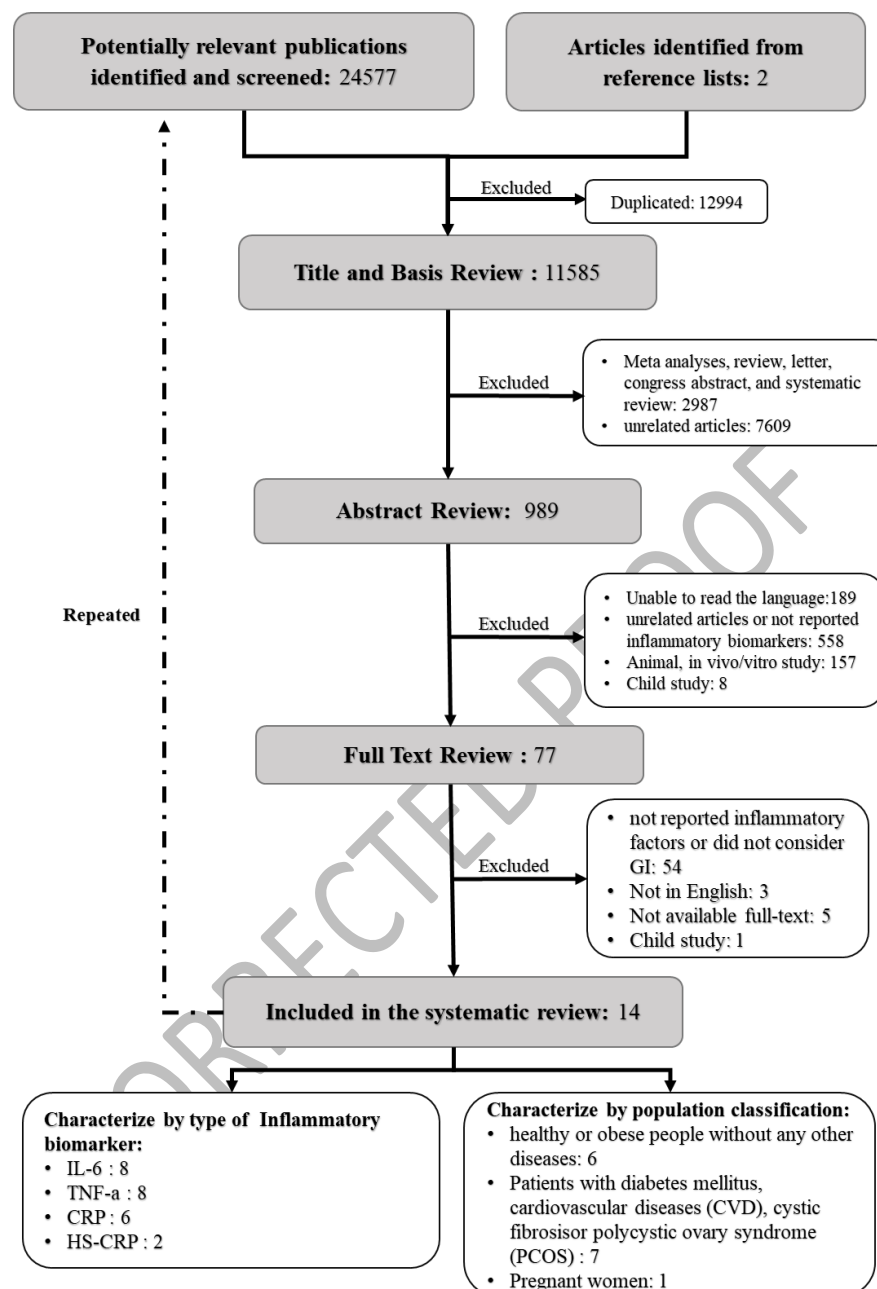
studies for which the full text was unavailable, and 6) studies published in languages that the authors could not read. The main reason for excluding GL was its potential confounding effect on inflammation due to the amount of carbohydrate consumed. Ultimately, only studies that directly evaluated the effect of GI on inflammatory biomarkers were included in this review.

### Study Selection

During the study selection process, researchers independently reviewed all papers, and the final findings were merged. A total of 24,577 articles were found in databases and Google Scholar. Three researchers (KE, PM, and AV) initially reviewed each article's title and general information to identify animal studies, children's studies, and review articles. Meta-analyses, reviews, letters, systematic reviews, animal studies, and studies conducted on children were excluded. The abstracts of 989 papers were thoroughly reviewed by three reviewers (PM, PZSh, and KS). Nine hundred and twelve articles met the exclusion criteria, and seventy-seven articles were deemed eligible for full-text review, which was conducted by three reviewers (PZSh, MR, and MRSh). The final number of relevant articles suitable for this systematic review was fourteen. Two judges (FK and RR) were involved throughout the review process. The review process was repeated once more by three reviewers (KE, PM, and AV), and no significant differences were found between the two rounds. A full description of this process is provided in Figure 1.

### Risk of Bias Assessment

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS) checklist was used to assess the risk of bias and visualized using the robvis tool. The assessment is structured around seven domains: pre-intervention biases (D1: Confounding), during-intervention biases (D2: Selection of participants, D3: Classification of interventions), and post-intervention biases (D4: Deviation from intended interventions, D5: Missing data, D6: Measurement of outcomes), as well as biases in the selection of reported results (D7: Selection of reported results).



**Figure 1.** Flow diagram of study selection. GI: Glycemic Index, GL: Glycemic Load, IL-6: Interleukin-6, IL-1: Interleukin-1, TNF- $\alpha$ : Tumor Necrosis Factor Alpha, CRP: C-Reactive Protein, HS-CRP: High Sensitive C-Reactive Protein, N/A: Not applied

## Results

Of the 14 studies included in this review (28-40) which also encompassed one MSc thesis (41) seven studies (28, 29, 32, 33, 36, 37, 39) were conducted on individuals with diabetes mellitus, cardiovascular diseases (CVD), and polycystic ovary syndrome (PCOS). Six studies (30, 31, 34, 38, 40, 41) investigated healthy or obese

individuals without any underlying diseases, and one study (35) focused on pregnant women.

Of the reviewed studies, nine (29-36, 40, 41) evaluated the impact of GI on inflammatory biomarkers, while five studies (28, 33, 37, 39, 40) assessed both GI and GL. The inflammatory markers studied included IL-6 in eight studies (30, 35-41), TNF- $\alpha$  in eight studies (28, 32, 35-38,

40, 41), CRP in six studies (30, 31, 33, 34, 40, 41) and HS-CRP in two studies (29, 39). The risk of bias for these studies is illustrated in Figure 2, with a comprehensive summary of the findings in Table 2.

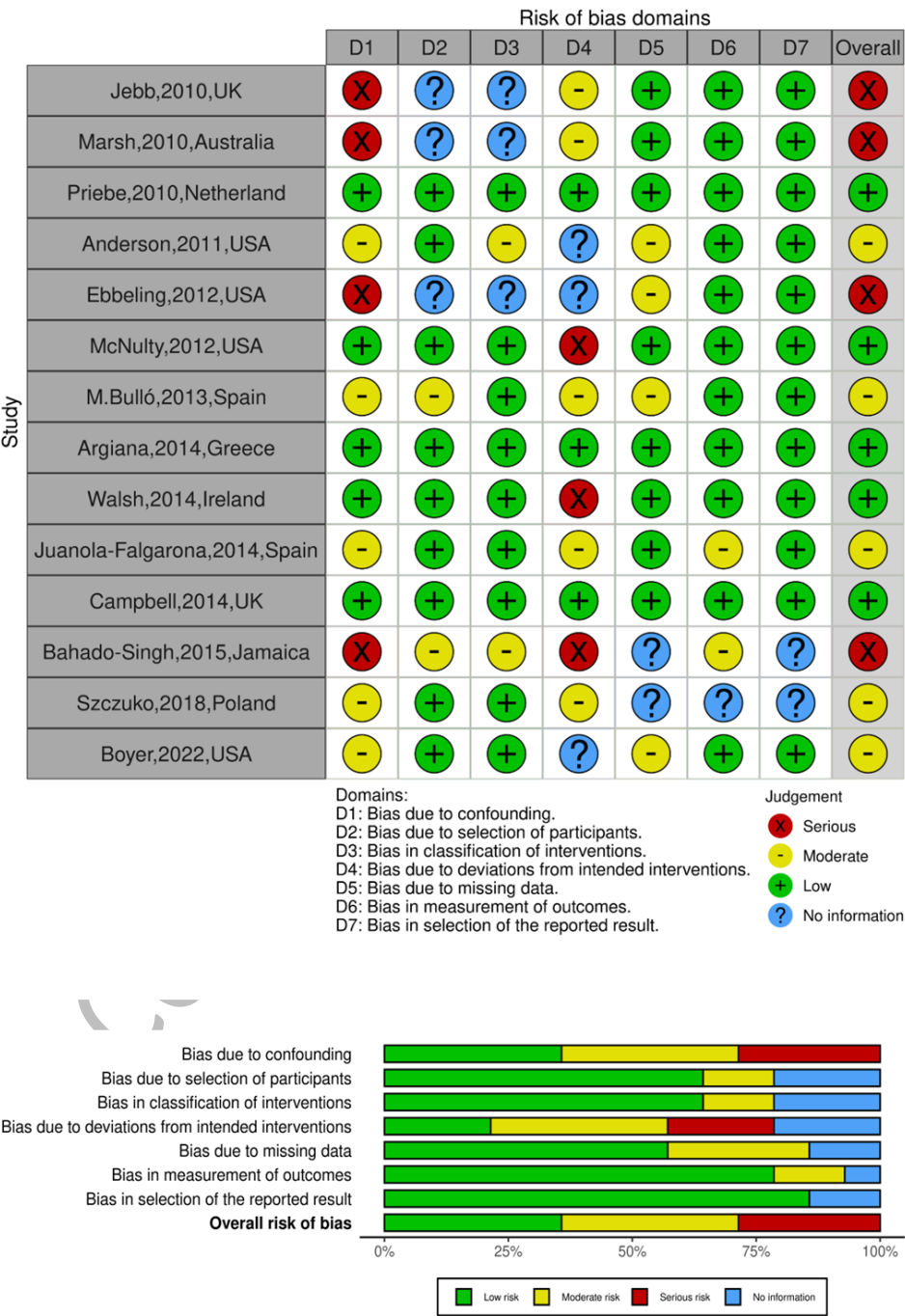


Figure 2. The risk of bias assessment visualized by robvis (visualization tool).

**Table 2.** Summarize findings by publishing order.

Study (author, year, country)	Study design	Study group	Population (number, gender, and age)	Inflammatory factors analyzed	Duration of follow-up	Outcome Mean $\pm$ SD	Outcome P-value	Confounding factors adjustment	Conclusion
Jebb, 2010, UK (35)	dietary intervention	Healthy people	548 (230 men/318 women, mean age for men 52 $\pm$ 10 and women 51 $\pm$ 9)	CRP (mg/L)	24 weeks	<div> <div> <div>HS/HGI (N=85)</div> <div>HM/H (N=11)</div> <div>HM/LGI (N=16)</div> <div>LF/H (N=16)</div> <div>LF/L (N=21)</div> </div> <div>CRP (mg/L)</div> <div> <div>base line</div> <div>Foll ow-up</div> <div>Per centa ge chan ge</div> </div> </div>	0.86	Adjusted for sex, center, ethnicity, baseline waist circumference, (log)HDL cholesterol, and age	No significant relation between GI and CRP in groups
						0.7 (0.16, 2.3)			
						0.5 (0.20, 2.0)			
						0.4 (0.14, 1.1)			
Marsh, 2010, Australia (34)	dietary intervention	overweight and obese premenopausal women with PCOS	96 (0 men/96 women, mean age: 30.1)	CRP (mg/L)	12 months or until they achieved a 7% weight loss	<div> <div>Low GI (n=50)</div> <div>CHD (n=46)</div> <div>CRP (mg/L) change</div> </div>	0.24	Adjusted for baseline (weight and body fat) or baseline and metformin (other variables) by using the general linear model ANOVA	No significant relation between GI and CRP in groups
						Baseline			
						5.3 $\pm$ 0.8			
						4.6 $\pm$ 0.5			
Priebe, 2010, Netherland (39)	randomized Cross over study	Healthy people	10 (10men/0 women, age 21 $\pm$ 2.0)	IL-6 (pg/mL) TNF-a (pg/mL)	60 minutes before consumption to 240 minutes after consumption	<div> <div>Fasting concentration</div> <div>0-2 h Postprandial concentration</div> <div>0-4 h Postprandial concentration</div> <div>IL-6 (pg/mL)</div> </div>	<0.05	N/M	non-digestible carbohydrate rate (generally low GI carbohydrate rate) increases inflammatory biomarkers less than digestible carbohydrate rate (high GI carbohydrate rate)
						Low GI (n=10)			
						7.0 $\pm$ 0.8			
						5.2 $\pm$ 0.8			
						High GI (n=10)	<0.05		
						13.1 $\pm$ 4.2			
						15.0 $\pm$ 4.5			
						19.7 $\pm$ 5.1			
						TNF-a (pg/mL)	<0.05		
						Low GI (n=10)			
						5.7 $\pm$ 1.9			
						5.5 $\pm$ 1.8			



Study (author, year, country)	Study design	Study group	Population (number, gender, and age)	Inflammatory factors analyzed	Duration of follow-up	Outcome Mean $\pm$ SD	Outcome P-value	Confounding factors adjustment	Conclusion
						High GI (n=10) 6.6 $\pm$ 1.8 6.7 $\pm$ 1.7 7.8 $\pm$ 2.1			
Andersson, 2011, USA (27)	cohort study	Aged healthy people	1751 (percent age of men is different from 36.7% to 83.9% in groups, aged 70–79)	IL-6 (pg/mL) CRP (mg/mL) TNF- $\alpha$ (pg/mL)	from baseline and year 2 of the study	reported GI of groups 50.2 (n=31) 54.4 (n=19) 5.2 (n=8) 55.8 (n=70) 58.8 (n=84) 59.6 (n=258) IL-6 (pg/mL) Geometric mean 2.1 (n=2) 1.6 (n=9) 1.1 (n=9) 1.1 (n=8) 1.1 (n=8) 1.7 (n=8) CRP (mg/mL) Geometric mean 1.5 (n=5) 1.6 (n=6) 1.1 (n=8) 1.1 (n=8) 1.1 (n=8) 1.7 (n=8) TNF- $\alpha$ (pg/mL) Geometric mean 2.9 (n=2) 2.9 (n=2) 3.2 (n=2) 3.2 (n=2) 3.2 (n=2) 3.0 (n=2)	N/M N/M N/M	Adjusted for gender, age, and race	no analyses were performed according to the GI
Ebbeling, 2012, USA (32)	controlled 3-way crossover study	overweight and obese young adults	21 (13 men/8 women, aged 30.3)	CRP (mg/L)	Not clear but was During Weight-Loss Maintenance	Pre-Weight-Loss Baseline 1.75 (0.44 to 4.61) Low Fat (n=21) -0.78 (0.38 to 1.92) Low Glycemic Index (n=21) -0.76 (0.50 to 2.20) Very Low Carbohydrate (n=21) -0.87 (0.57 to 2.69)	Overall= 0.13 Trend= 0.05	None but Rank transformed for analysis	No significant relation between GI and CRP in groups but the trend of change was significant
McNulty, 2012, USA (41)	dietary intervention	overweight and obese women	20 (0 men/20 women, aged 30.3)	TNF- $\alpha$ (pg/mL) IL-6 (pg/mL) CRP (mg/L)	Less than a week (24 to 48 h)	Low GI (n=10) High GI (n=10) TNF- $\alpha$ (pg/mL) Pre-exercise 1.13 $\pm$ 0.18 1.79 $\pm$ 0.43 Post-exercise 1.06 $\pm$ 0.11 1.67 $\pm$ 0.26 24 h 0.98 $\pm$ 0.13 1.20 $\pm$ 0.13 48 h 1.12 $\pm$ 0.16 1.32 $\pm$ 0.18 IL-6 (pg/mL) Pre-exercise 2.28 $\pm$ 0.52* 3.05 $\pm$ 0.61 Post-exercise 3.0 $\pm$ 0.52* 3.96 $\pm$ 0.59 24 h 2.59 $\pm$ 0.49* 2.84 $\pm$ 0.50 48 h 2.23 $\pm$ 0.39* 2.64 $\pm$ 0.51 CRP (mg/L) Pre-exercise 2.06 $\pm$ 0.48 2.46 $\pm$ 0.86 Post-exercise 2.00 $\pm$ 0.51 2.87 $\pm$ 1.06 24 h 2.23 $\pm$ 0.36 2.81 $\pm$ 1.13 48 h 2.13 $\pm$ 0.38 2.40 $\pm$ 0.77	0.24 0.42 0.59	N/M	no significant relation was found in both TNF and CRP but IL-6 was significantly decreased in the low GI group

Study (author, year, country)	Study design	Study group	Population (number, gender, and age)	Inflammatory factors analyzed	Duration of follow-up	Outcome Mean $\pm$ SD	Outcome P-value	Confounding factors adjustment	Conclusion
M. Bulló2, 2013, Spain (38)	cohort dietary intervention	no cardiovascular disease and met one or more of the two following criteria: three or more cardiovascular risk factors, or type 2 diabetes mellitus	568, Q1: 126 Q2: 129 Q3: 128 Q4: 128 (Men: 227/Women: 284, men aged 55-80 years and women 60-80 years)	IL-6 (pg/mL) TNF- $\alpha$ (pg/mL)	1 year	Q1 (n=126)      Q2 (n=129)      Q3 (n=128)      Q4 (n=128)	0.969	Adjusted for sex, age, changes in waist circumference, changes in body mass index, intervention group, physical activity in leisure time, smoking, insulin use, presence of type 2 diabetes mellitus, w-3 fatty-acid intake, and fiber	a significant relation between TNF- $\alpha$ and GI at the baseline but changes in GI after 1 year did not have any significant relation between GI and both IL-6 and TNF
						<b>IL-6 (pg/mL) change relative to the change in quartile (Q) 1</b>			
						<b>TNF-<math>\alpha</math> (pg/mL) change relative to the change in quartile (Q) 1</b>	0.798		
						0      -0.04 (-5.45 to 5.36)      -2.49 (-7.93 to 2.94)      1.63 (-3.99 to 7.25)			
Argian a, 2014, Greece (40)	dietary intervention	type 2 diabetes	61 (Men: 27/ women: 31, age: 61.3 and 63 for Low GI/GL and Controls groups respectively)	HS-CRP ( $\mu$ g/mL) IL-6 (pg/mL)	12 weeks	Low GI/GL (n=28)      Controls (n=31)	0.007	N/M	GI has a significant relation with HS-CRP but no significant change was found in IL-6
						<b>HS-CRP (<math>\mu</math>g/mL) change</b>			
						<b>IL-6 (pg/mL) change</b>	0.718		
						-0.1 $\pm$ 0.3      0.7 $\pm$ 0.5			
Walsh, 2014, Ireland (36)	dietary intervention	Pregnant women	621 (0 men/ 621 women, age not mentioned)	TNF- $\alpha$ (pg/mL) IL-6 (pg/mL)	early pregnancy and to 28 weeks	Intervention Group      Control Group	NS	N/M	no significant relation was found between GI with either IL-6 or TNF- $\alpha$
						<b>TNF-<math>\alpha</math> (pg/mL)</b>			
						28 weeks      5.36 (3.19-7.83)      4.65 (3.09-7.71)			
						Cord      5.62 (0.58-9.2)      5.08 (0.88-8.49)			
						<b>IL-6 (pg/mL)</b>			
						First trimester      9.70 (4.17-21.1)      9.48 (4.38-26.26)			
						28 weeks      9.98 (5.38-20.8)      9.37 (4.21-22.34)	NS		
						Cord      10.95 (3.55-29.0)      9.17 (3.06-23.91)			
Juanola-Falgarona,	Controlled clinical trial	overweight and obese adults	122 (men: 25/women: 97,	IL-6 (pg/mL)	6 month	Low GI (n = 41)      High GI (n = 40)      Low Fat diet (n = 40)	0.457	N/M	No significant relation between
						<b>CRP (mg/mL)</b>			



Study (author, year, country)	Study design	Study group	Population (number, gender, and age)	Inflammatory factors analyzed	Duration of follow-up	Outcome Mean $\pm$ SD	Outcome P-value	Confounding factors adjustment	Conclusion
2014, Spain (31)			aged 42.5 to 44.1 in groups)	CRP (mg/mL)	Base line 6-m change	2.99 $\pm$ 4.34 -20.19 $\pm$ 1.78	3.58 $\pm$ 6.25 -20.07 $\pm$ 2.74	3.70 $\pm$ 5.59 -20.04 $\pm$ 1.72	groups for both IL-6 and CRP
						IL-6 (pg/mL)			
					Base line 6-m change	1.67 $\pm$ 1.18 -20.27 $\pm$ 0.86	1.36 $\pm$ 0.90 0.12 $\pm$ 0.91	1.66 $\pm$ 1.11 -20.01 $\pm$ 0.72	0.162
Campbell, 2014, UK (37)	dietary intervention	type 1 diabetes	10 (10 men/0 women, aged 27 $\pm$ 5)	IL-6 (pg/mL) TNF- $\alpha$ (pg/mL)	60 minutes before consumption to 180 minutes after consumption	time -60 meal 60 120 180	Low GI (n=5) 5.8 4.8 4.2 4.5 <sup>a</sup> 4.2 <sup>b</sup>	High GI (n=5) 6 5.2 5.3 8.7 <sup>a</sup> 8.2 <sup>b</sup>	<0.05 N/M
						TNF- $\alpha$ (pg/mL)			
					-60 meal 60 120 180	5.8 4.5 3.6 <sup>c</sup> 4.2 <sup>d</sup> 3.8 <sup>e</sup>	5.6 4.5 6.7 <sup>c</sup> 6.6 <sup>d</sup> 6.1 <sup>e</sup>	<0.05	There is a significant relationship between GI with IL-6 and TNF- $\alpha$
Bahadur Singh, 2015, Jamaica (30)	dietary intervention	overweight people with type 2 diabetes	53 (24 men/29 women, mean age 42 $\pm$ 2.0 years)	HS-CRP (mg/dL)	24 weeks	Baseline Difference between week 12 and baseline Difference between week 24 and baseline %	Low-Intermediate GI 1.36 $\pm$ 0.21 -0.65 $\pm$ 0.19 -0.52 $\pm$ 0.17 -38.24	Conventional Diet/ High GI 1.12 $\pm$ 0.30 -0.33 $\pm$ 1.09 -0.17 $\pm$ 0.31 -15.18	<0.05 Adjusted for age, BMI, smoking, alcohol consumption, history of hypertension, history of hypercholesterolemia, and duration of diabetes.
Szczuko, 2018, Poland (33)	Dietary Intervention	Women with PCOS	22 (20 men/2 women, age 26.76 $\pm$ 5.08)	TNF- $\alpha$ (pg/mL)	3 months	before 59.69 (35.79–104.4)	after 57.626 (43.48–98.83)	NS	No significant relationship between before and after intervention
						TNF- $\alpha$ (pg/mL)		NS	

Study (author, year, country)	Study design	Study group	Population (number, gender, and age)	Inflammatory factors analyzed	Duration of follow-up	Outcome Mean $\pm$ SD	Outcome P-value	Confounding factors adjustment	Conclusion
Boyer, 2022, USA (29)	Dietary Intervention	Premenopausal women at high genetic risk of breast cancer	137 (10men /137women, (mean age =34.2)	TNF- $\alpha$ (pg/mL)		Mean of the population = $4.6 \pm 1.3$ $\beta$ without adjustment = 0.008, $p > 0.05$ $\beta$ with adjustment = 0.005, $p > 0.05$		BMI and total energy intake	No significant association between GI change before and after the intervention

1. To convert nmol/L to mg/L CRP, it is multiplied by 9.524

2. Population quartile to their glycemic index at baseline.

3. Outcome's mean is extracted from the article chart by JavaTpoint software (Approximate)

4. The sampling of studies is 1:1 grouping but the specific size of each group was not mentioned in the text.

\* Was significant within-group after the intervention

outcomes with the same alphabet (<sup>abcd</sup>) are significant to each other

N/M: Not Mentioned, GI: Glycemic Index, GL: Glycemic Load, IL-6: Interleukin-6, IL-1: Interleukin-1, TNF- $\alpha$ : Tumor Necrosis Factor Alfa, CRP: C-Reactive Protein, HS-CRP: High Sensitive C-Reactive Protein, CHD: conventional healthy diet, PCOS: polycystic ovary syndrome, NS: not significant without P.value

Among the studies that explored the relationship between GI and inflammatory biomarkers, five studies—mainly clinical trials with a total sample size of 155 and a mean sample size of 31—identified a significant association between GI and at least one inflammatory biomarker (35-39). In contrast, seven studies, primarily population-based interventions with a total sample size of 3,300 and a mean sample size of 471, found no significant relationship between GI and inflammation (28-34). One study observed a significant association at baseline, but this was not maintained upon follow-up (37). Additionally, one study (40) did not perform any statistical analyses regarding the relationship between GI and inflammatory biomarkers.

The findings highlight several important considerations, including the influence of dietary patterns on the inflammatory effects of GI, the significance of study design, and the variability in GI's impact. While most studies with larger sample sizes did not find a strong association, a detailed review suggests that GI may have a minor effect on inflammation. The heterogeneity of the studies, methodological differences, and confounding factors complicate the interpretation of these results. Despite the inconclusive evidence, the authors propose a potential link between GI and inflammation

while acknowledging the limitations of the studies reviewed. These limitations should be carefully considered in future research exploring the relationship between GI and inflammatory biomarkers.

## Discussion

The reviewed studies generally support the authors' hypothesis. However, the studies are heterogeneous, and differences influence their findings in methodology and confounding factors. Despite the majority of studies with larger sample sizes showing no significant association, a detailed review suggests that GI may have a minor effect on inflammation. However, the complexity of GI and the lack of sufficient studies with consistent findings prevent us from providing a definitive answer to this question. In this review, the authors propose a possible link between GI and inflammation and outline the main limitations that should be considered in future studies.

In 2010, findings from a multicenter diet intervention study reported no significant differences in CRP levels between groups, both before and after adjustment (34). However, further analysis within the study revealed two completely different effects of GI on CRP—one positive and one negative—associated with two

distinct diet patterns. The findings led to the hypothesis that diet patterns, particularly fat content, can influence the effect of GI (34). This is the first confounder identified in the study that was not adequately addressed. It is worth noting that the potential effect of food components and GL on GI and inflammatory responses has been reported several times before (9, 10, 26).

According to reports from a cohort study, diet patterns with higher GI scores were associated with slightly higher TNF- $\alpha$  and CRP levels than lower GI groups (40). However, no in-group analysis was performed in this study. A key finding from this study is that GI may vary significantly depending on the diet patterns, supporting previous hypotheses (9, 10, 26). For example, in this study, diet patterns involving sweets and desserts had a lower GI than those involving refined grains and breakfast cereals, which were believed to have a higher GI (40). This represents another significant limitation for studies on GI and GL. Based on the current research, it is recommended to consider the population's diet patterns and the consumption of unhealthy foods—characterized by a higher inflammatory index and lower GI—as confounders. However, it must be acknowledged that controlling a population's diet in a real-life environment, which contains multiple confounders that affect both GI (e.g., diet) and inflammation (e.g., stress, physical activity, injuries), is nearly impossible. Therefore, a high risk of bias can be expected in population-based and cohort studies investigating GI.

Designing studies with appropriate methodology that can isolate samples from confounders presents a significant challenge. While such studies can provide suitable laboratory conditions, their main limitations often include small sample sizes and short follow-up periods. Some studies with strong methodologies fall into this category (28, 32, 33). However, three studies with well-controlled, low-bias protocols demonstrated a significant direct relationship between GI and inflammation despite their small sample sizes (31, 36, 38). In all of these studies, participants adhered to a closely monitored diet during the assessment, highlighting the importance of controlling confounders over the sample size (31, 36, 38). Additionally, one study showed that providing linear graphs for small sample-sized studies could offer valuable insights (38). These findings underscore the

significant impact of confounders on study results.

In another study with a large population, a 137-item Food Frequency Questionnaire (FFQ) was used to assess dietary intake and GI (37). This study, based on the Brand-Miller GI table (27), found a significant association between TNF- $\alpha$  and GI at baseline (P-ANOVA = 0.046) (37). However, no significant differences were observed after a one-year intervention between GI and IL-6 or TNF- $\alpha$  (37). The main reason for this discrepancy is the study's methodology, which involved low-inflammatory diet patterns in the groups (42-44). This study compared two potential anti-inflammatory diet patterns, which could have influenced the results. Nonetheless, the nature of the survey may also have impacted the findings, similar to previous population-based studies.

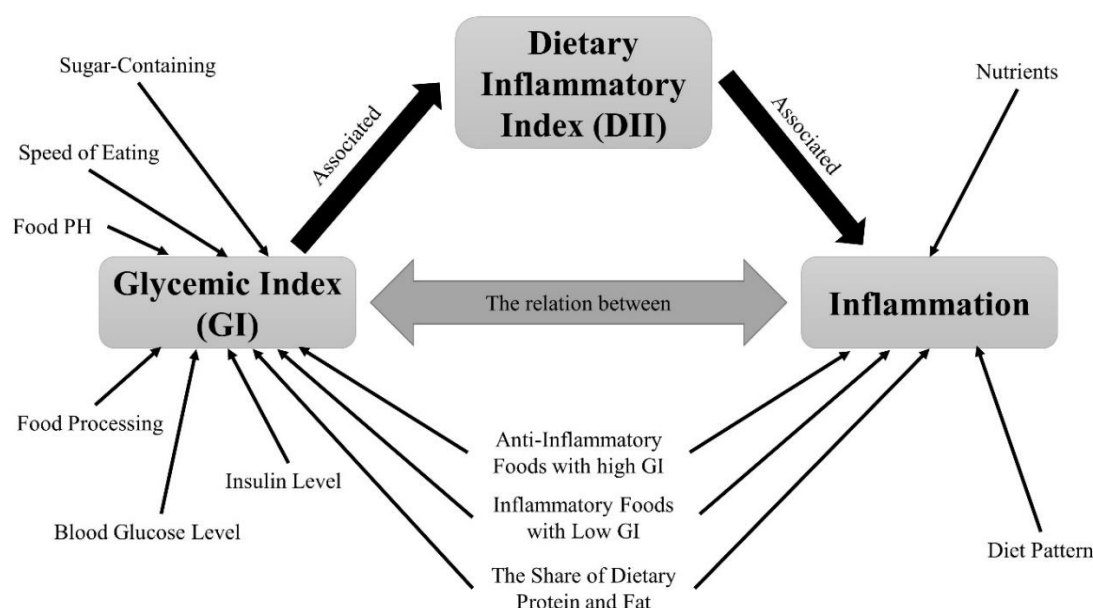
One of the notable findings in the Bahado-Singh et al. study (29) showed a 38.24% decrease in HS-CRP levels in the low-intermediate GI group, compared to a 15.18% decrease in the high GI group. Despite the decline in both groups, the reduction in the low-intermediate GI group was significantly smaller than in the high GI group ( $p < 0.05$ ). However, the study did not explain the anti-inflammatory effect observed in both high and low-intermediate GI diets. Although both groups followed the same diet during the assessment, the decrease in HS-CRP could have been influenced by other anti-inflammatory components in the diets. Nevertheless, the low GI diet demonstrated a more potent anti-inflammatory effect. The adherence of the sample population to their diet plan and environmental factors played a key role in these findings.

These confounding effects can influence the current understanding of the topic. Inflammatory biomarkers are more sensitive than outcomes like disease incidence, which may explain the variability in findings. Despite supporting data on the effect of GI on various diseases (7, 9, 10, 15-21, 45, 46), results on inflammatory biomarkers vary widely. A meta-analysis shows a significant difference between low and high GI groups in CRP levels for both models in obese individuals with and without diabetes (47). At the same time, a meta-analysis by Milajerdi et al. found no inflammatory effect of GI, supporting the findings of Buyken et al. (26, 48). Conversely, another study demonstrated an association

between GI and oxidative stress (49). These discrepancies highlight the importance of sample size and the methodology used in selecting studies for systematic reviews. In general, the sample size of studies significantly impacts the weight of findings in meta-analyses. Consequently, the results of cross-sectional and population-based studies, which have limited control and a higher risk of bias, tend to outweigh those of controlled interventions. Therefore, it is recommended that future studies in this field focus on interventions in individuals within controlled conditions, with equal carbohydrate intake and similar characteristics.

Nevertheless, the most significant finding supporting the association between GI and inflammation was reported in the study by Yeon-Soo et al. in 2018 (50). In this study, an association was found between GI and the Dietary Inflammatory Index (DII), which was developed by Dr. Shivappa and Dr. Hebert (51-54) to assess dietary inflammatory potential. This study, along with the reported effect of GI on CRP by Schwingshackl et al. (47), suggests a need to reconsider the effect of GI on inflammation, as previously reported by Milajerdi et al. (26).

One of the main weaknesses of the GI is related to its nature, which, if not adequately controlled, increases the risk of bias. Factors such as food processing, sugar content, other nutrients, food pH, speed of eating, blood glucose levels, and insulin levels can all affect the body's GI response, as illustrated in Figure 3 (12-14, 55-57). Another significant weakness of the GI is its food classification pattern (12-14). In this pattern, some pro-inflammatory foods—such as pizza (GI=39), fructose (GI=15), chocolate (GI=40), ice cream (GI=51), soft drinks/soda (GI=59), and potato crisps (GI=56)—are classified as low to moderate GI foods, while some fruits—like pineapple (GI=59), mango (GI=51), and watermelon (GI=76)—have a higher GI (12-14). Considering these issues, it is possible that an unhealthy diet pattern could have a lower GI than a healthier one, but further research is needed to confirm this hypothesis. These factors represent potential confounders that can influence the results of population-based studies, although they can be controlled in isolated conditions.



**Figure 3.** The possible direct and indirect confounders of the effect of GI on inflammatory biomarkers

Based on the findings and considering the limitations, conducting a well-designed GI study presents several complications that must be

addressed. Among all food components, it seems that diet patterns have the most confounding effect, though further investigation is still needed

(3, 6, 29, 34). Continued follow-ups in controlled clinical trials, with isolated conditions or ensuring participants' diet adherence, could also be beneficial. Additionally, studies to explore the association between diet patterns and GI are recommended. To better understand the effect of GI on inflammation, using more homogenous populations and controlling for differences in diet patterns—which can introduce biases—would provide considerable benefits. Nevertheless, a dietary pattern high in fruits, vegetables, fish, poultry, legumes, and whole grains, and low in red and processed meats, sweetened beverages, sweets, refined grains, and fried potatoes, has been linked to lower levels of inflammatory biomarkers, regardless of GI and GL (3, 5, 6, 40). Therefore, understanding the association between GI and inflammation may benefit clinical settings, particularly in hospitals and intensive care units. This could inform the design of oral or enteral formulas to control inflammation and glycemic responses in these settings and for sensitive patients who need to follow specific diets at home.

The strength of this study lies in the perspectives of the reviewers. At each step, at least two researchers with differing opinions reviewed the studies, providing a fresh perspective and potential hypotheses for further research. However, the main weaknesses of this study are related to the nature of GI and the lack of sufficient studies. Another limitation was the absence of statistical analysis. Nevertheless, the authors recognized that the current findings on GI are not suitable or homogenized for this purpose. Given the unclear effect of dietary patterns in the reviewed studies, any analysis could introduce bias, though it may still provide a statistically specific answer to this issue.

## Conclusion

Despite research in this field, the findings of studies remain inconsistent, and numerous confounders can affect the results. There is evidence supporting a slight effect of GI on inflammatory biomarkers. Based on the available evidence, diet and underlying factors can significantly influence the relationship between GI and inflammation. However, further research is needed to establish a clear link between GI and inflammation. Specifically, studies should focus on homogenized populations with similar diet patterns, and continuous monitoring through

follow-up studies is recommended. Given the previous meta-analyses on this subject, it is likely that diet-related biases, which are not statistically recognized, may have influenced the findings.

## Declarations

### **Ethics Approval and Consent to Participate**

The protocol is approved by an in-house committee at Varastegan Institute for Medical Sciences

### **Consent for Publication**

The earliest version of this publication has been pre-printed at <https://doi.org/10.21203/rs.3.rs-1558724/v1>, which was significantly improved after several revisions.

### **Availability of Data and Materials**

Data is available upon reasonable request.

### **Conflict of Interest**

The authors of this paper declare no conflict of interest.

### **Funding**

This study received no funding

### **Authors' Contributions**

All authors participate in the search and review of the papers described in the method. KE, PM, MRSH, and AV drafted the paper, RR and FK made the final revision, and RR and MRSH accepted the responsibilities of the corresponding authorship. MRSH submitted.

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### **Abbreviations**

Interleukins-1: IL-1

Interleukins-6: IL-6

Interleukins-10: IL-10

Tumor Necrosis Factor- $\alpha$ : TNF- $\alpha$

C-Reactive Protein: CRP

High-Sensitive C-Reactive Protein: HS-CRP

Glycemic Index: GI

Glycemic Load: GL

Food Frequency Questionnaire: FFQ

Preferred Reporting Items for Systematic Review and Meta-analysis: PRISMA



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