ORIGINAL ARTICLE

Impact of exercise on epithelial injury of gastrointestinal membrane associated with levels of circulating I-FABP - A systematic review and meta-analysis of randomized control trial

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ABSTRACT

Aim: Intense exercise promotes intestinal injury in the gastrointestinal tract of humans and a substantial upsurge in intestinal permeability indicating gut barrier dysfunction. **Design:** Systematic review and meta-analysis **Objective:** The goal line for this systematic review and meta-analysis was to investigate the consequence of a strenuous workout session on Intestinal epithelial cells (IECs) injury of gastrointestinal membrane and permeability in healthy persons. **Methods:** Through May 2023, PubMed, EMBASE, Scopus, and Web of Science were searched. Studies were included evaluating intestinal Fatty Acid Binding Protein (I-FABP) of gut permeability and gut cell injury following a solitary strenuous workout. **Results:** 18 studies showed a mean difference of 488.36 [95% CI 280.35; 696.37] in I-FABP post-exercise using a random effects model. The studies were heterogeneous, with a 95% prediction interval of − 427.52 to 1404.24. I-FABP, as a measure of gut injury, had a significant and moderate impact magnitude in disturbing the epithelial lining of the intestinal membrane. **Conclusion:** This project's decisions establish that a sole strenuous exercise session elevates gut permeability and damage to healthy contributors. The study has been registered with PROSPERO (CRD42023387126).

KEYWORDS

Intestinal Fatty Acid-Binding Protein; Biological Markers; Exercise Intensity; Epithelial cells; Intestinal Permeability; Gastrointestinal Mucosa Injury

INTRODUCTION

Intestinal damage and loss of barrier integrity are critical issues, especially for athletes, as they cause abdominal discomfort, impaired nutrient absorption, and delayed recovery. Mucosal damage is exacerbated by microbial

products and digestive enzymes penetrating the submucosa due to a compromised gastrointestinal (GI) epithelial lining (1).

Strenuous exercise further disrupts epithelial integrity, enabling endotoxins to enter circulation and trigger dysregulation (2). Additionally, reactive oxygen species (ROS) generated under hypoperfusion and reperfusion (3) contribute to oxidative stress, damaging cellular components and worsening GI dysfunction (4).

Markers of intestinal permeability, such as lactulose absorption and circulating intestinal fatty acid binding protein (I-FABP), are increasingly recognized as reliable indicators of gut injury (5). I-FABP, a 14–15 kDa cytosolic protein highly expressed in enterocytes, is rapidly released into circulation upon epithelial damage (6). Elevated levels are strongly associated with intestinal barrier compromise, making it a promising biomarker for diagnosing epithelial injury and gut hyperpermeability ("leaky gut") (7).

Aims & Objectives

- To systematically evaluate the role of I-FABP as a biomarker for intestinal epithelial damage.
- To assess the diagnostic accuracy of I-FABP in differentiating gastrointestinal epithelial injuries.
- To synthesize existing evidence through meta-analysis for validating I-FABP in clinical and exercise-related GI barrier dysfunction.

Material & Methods

The core intention of the project involves inspecting the outcome of intense exercise contributing to compromised intestinal membrane permeability in healthy volunteers by estimating the level of I-FABP, which is reported to be released in blood upon damage to gut cells.

2.1 Study Protocol: The systematic review and meta-analysis agree with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8). This work was registered with PROSPERO (CRD42023387126).

2.2 Search Strategy: The PICO framework for the systematic reviews was deployed to create thorough literature search strategies (Supplementary S1; Table 1). With the assistance of electronic and manual pursuits in literature references, appropriate studies were recognized. Various databases like Embase, Scopus, PubMed and the Web of Science were explored via automated searches up to May 2023 for the applicable studies. These databases with suitable Boolean operators, generic terms, keywords, and medical subject headings (MeSH): I-FABP, exercise, intestinal permeability, or gastrointestinal membrane disintegrity were explored methodically. No linguistic and periodic limitations were applied during the literature search. The search approach was peer revised by another author according to the Peer Review of Electronic Search Strategies checklist (9).

2.3 Selection Process: NR and CP screened databases. Acquired studies from electronic databases were carried across to Endnote (version 20), a referencing program. Articles in replica were filtered by referencing software first, then manually. Following that, duplicates were marked and eliminated. The full text of all the articles was retrieved for further screening. The evaluation consisted of two leaps: firstly, the preliminary pieces of literature were obtained and individually reviewed by each investigator (NR and MAK). Then, the disputes were debated and settled by consensus (AP), allowing the final data to be translated.

2.4 Selection Criteria: We included randomized clinical studies reporting data on confirmed participants without prior evidence of intestinal damage, free of illness symptoms (all genders, all age groups), intestinal cellular damage/injury induced by exercise, changes in intestinal permeability, gut barrier dysfunction, change in the levels of I-FABP without any supplementation during exercise (running, cycling, swimming, and so forth.) without any geographical restriction (Table 1). English language, human studies, published and unpublished data. The studies in duplicate journals providing information on similar parameters were incorporated just once, with only the utmost extensive data included and published lately. Excluded articles include reporting I-FABP changes with any supplementation intervention or pre-

treatment, poster publications, letters to the editor, review articles, conference papers, qualitative policy, systematic reviews and meta-analyses, narrative reviews, case reports and opinion reports, and publications with inadequate writing of data and full-text articles without retrieval access. The training subject's body composition was not restricted in any way.

2.5 Data Extraction: Data was retrieved regarding subsequent details: author, publication year, study design, volunteers, age, exercise category, workout duration and specification, I-FABP measure points at different intervals, and other critical features of the study. The writers were contacted to share the values of I-FABP for studies that did not report the direct value. WebPlotdigitizer 4.6 (https://apps.automeris.io/wpd/) was used to estimate the I-FABP range from the studies with data presented in graphical format. Data presented in another format (Mean ± SEM) was converted to Mean ± SD wherever possible. The value of standard error was changed to standard deviation using formular; $SD = SE \sqrt{n}$ (10). When the median and interquartile range (IQR) were presented, revised techniques from Wan et al. were utilized to translate the data into Mean and SD (11).

2.6 Quality Assessment: The qualitative assessment of the included studies was done through RoBv2.0 via Cochrane Collaboration intended for randomized controlled trials. Bias was evaluated as a judgment (high risk, low risk, some concerns or no information) for distinct foundations from 5 domains (selection, performance, attrition, reporting, and others) (12). Two authors (NR and MAK) independently evaluated the retrieved articles. The issue was resolved with mutual consent after discussion in case of conflict.

2.7 Statistical Analysis: The elementary calculations were performed using Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA). Data recorded in the Excel sheet was extracted using R version 4.3.0 for further investigation. We synthesized the mean differences between the two sets of observations using an inverse variance method. Heterogeneity between articles was assessed by prediction interval, I^2, τ, and τ^2, in which the percentage of variability was determined (not sampling error). The restricted maximum likelihood estimator is used for tau-squared, and the Q-profile method is used for the confidence interval of tau-squared.

The results were visualized using forest plots and drapery plots. Drapery plots avoid an arbitrary threshold of significance of 0.05 and plot the individual study estimates against a range of p-values (13).

For publication bias and small-study effects, we used a trim-and-fill contour-enhanced funnel plot alongside the Doi plot (14) and the LFK index (15). Leave-one-out meta-analysis (16) is a sensitivity analysis that shows the effect on the pooled estimate after excluding each study individually.

Figure 1. PRISMA flow chart of the SRMA

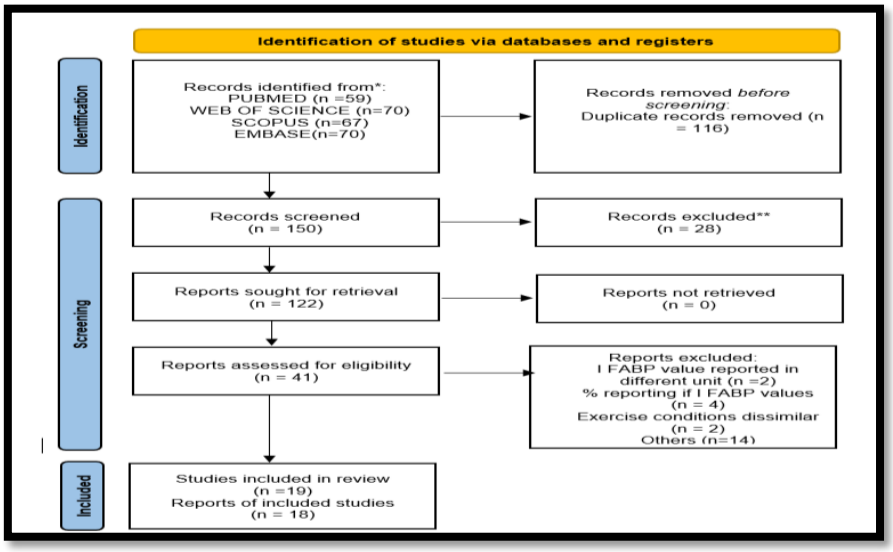


Table 1. Characteristics of the included studies to assess the impact of exercise on levels of I-FABP in SRMA

Study	Year	Design	Participants	Age (years)	Exercise		I-FABP measure points	Keynote	References
					Duration (minutes)	Type	Specifications			
Study 1	2017	Prospective clinical	9	18-45	90	running	10 km race at 80% of their best speed	at the baseline, at resting state, and then immediately after completing the run	This study finds that the serum concentrations of I-FABP were raised after the running test.	(17)
Study 2	2018	crossover design	14	20-35	60	cycling	at 70% Wmax in a hydrating state	At rest, at 30 minutes in between cycling, at 1 hour at the end of the exercise, and at various time intervals of post cycling i.e., 1.5-hour, 2-hour, 3-hour, 6-hour, 24 hours	Elevation in the values of I-FABP was observed in post-exercise	(18)
Study 3**	2017	randomized, counterbalanced design	10	18-22	47	running	Moderate running in a slightly warm and humid surrounding	Before the end and 1 hour, and 4 hours of post-run	Plasma I-FABP level was enhanced, indicating damage to the intestine.	(19)
Study 4	2014	placebo-controlled double-anonymized study	8	19-23	90	cycling	15-min cycling at 50 % HRR before and after 60 min of running (30 min at 80 % HRR, then a 30-min distance trial)	at baseline, after run 1, after run 2, and 5 h postexercise	I-FABP increased significantly from resting values to immediately postexercise	(20)
Study 5	2017	double-anonymized,	10	20-28	60	running	at 70% of maximum	pre- and postexercise and	I-FABP increased during exercise trials	(21)

Study	Year	Design	Participants	Age (years)	Exercise			I-FABP measure points	Keynote	References
					Duration (minutes)	Type	Specifications			
		placebo-controlled, randomized crossover design					oxygen saturation for 30°C and relative humidity (RH) of 40–45%.	45 minutes post-exercise		
Study 6	2017	counterbalanced	11	23-43	120	running	Eighteen rounds of 400 m run on a treadmill with 120% O2 max	Baseline, before and after each exercise set, as well as two hours later	A 72% increase in I-FABP occurred during HIIT from baseline levels to mean peak levels instantly after exercise, and a decrease occurred during recovery	(22)
Study 7	2018	Randomised cross over	12	NR	45	cycling	at 70% maximum VO2 in surroundings of either 30°C with 40% RH or 40% RH at 20°C	before and after completion of the exercise	A significant upsurge in the plasma I-FABP points was observed after cycling.	(23)
Study 8	2017	Randomised cross over	11	26-36	120	running	at 60% VO2 max in 35°C surrounding temperature	pre- and post-EHS, and during recovery	A significant increase in the level of I-FABP was observed at the post-exercise interval, which gradually lowered during the subsequent post-4 hr of exercise.	(24)
Study 9	2018	Randomised cross over	12	29-44	120	running	60% V̇O2 max in 35°C ambient temperature	pre, immediately, and one-hour post-exercise	I-FABP increased post-exercise	(25)
Study 10	2018a	Randomised cross over	10	25-37	120	running	environmental chamber in hot (35.4±1.8 °C and 26 ± 4% RH) and temperate (22.2±1.0 °C and	pre- and post-exercise, and during recovery	I-FABP significantly amplified pre- to post-exercise on HOT.	(26)

Study	Year	Design	Participants	Age (years)	Exercise			I-FABP measure points	Keynote	References
					Duration (minutes)	Type	Specifications			
							44±6% RH) ambient conditions			
Study 11	2018 b	Randomised crossover	10	25-39	120	running	within an environmental chamber in warm (30.2±0.4°C and 35±6% RH) and temperate (22.2 ± 1.0 °C and 44 ± 6 % RH) ambient conditions.	pre- and post-exercise, and during recovery	I-FABP significantly increased pre- to post-exercise in both trials.	(27)
Study 12	2018	Clinical trial	8	19	60	running	With 60 % maximum VO2	before (Pre), after (Post), 1hr (1-Post), and 4hrs after (4-Post) exercise.	Post hoc analysis indicated that I-FABP rose by 87% at the post and by 33% at 1-hour Post. in the Placebo state	(28)
Study 13	2011	Randomised Control Trial	20	22-24	60	cycling	at 70% of maximum workload capacity	every 10 minutes during exercise and post-exercise	I-FABP levels declined substantially in the first 10 minutes post-exercise and gradually decreased further until baseline I-FABP level was reached approximately 50 minutes after cycling	(29)
Study 14	2012	RCT	9	26-28	60	cycling	with Wmax at 70%	every 10 minutes during exercise and post-exercise	I-FABP enhanced after completing the trial	(30)
Study 15	2022	randomized, double-blind, placebo-	16	20-24	60	cycling	75% of maximal oxygen uptake	immediately pre- and post-exercise, 30 min,1, 2 and 4 h post-exercise	Compared to the intervention group, the place group has enhanced I-FABP level	(31)

Study	Year	Design	Participants	Age (years)	Exercise			I-FABP measure points	Keynote	References
					Duration (minutes)	Type	Specifications			
		controlled crossover								
Study 16	2022	Parallel group trial design	28	NR	120	both running and cycling	Run with 55% of maximal oxygen uptake and cycling at 55 % of maximal aerobic power in Tamb 35 °C and 22 % RH	Pre- and post-exercise	no significant difference in absolute pre- and post-exercise plasma I-FABP was observed	(32)
Study 17	2017	double-blind, placebo-controlled, crossover design	18	21-31	20	running	at a constant speed equivalent to 80% V̇O2 peak on a motorized treadmill with a 1% grade	pre- and post-exercise	Relative plasma I-FABP concentration soared from pre-experiment to post-experiment.	(33)
Study 18	2019	double-blind, placebo-controlled, crossover design	12	20-32	60	running	70% maximal aerobic capacity at 30°C with 60% RH	Prior and later to exercise, followed by one hour post-trial	The absolute plasma I-FABP concentration rose considerably from Pre-Ex to Post-Ex.	(34)

**(Not included in forest plot- excluded due difference in exercise condition not at ambient temp)

Abbreviations: HRR- heart rate reserve, RH- relative humidity, NR- not reported, T_{amb}- ambient temperature, $\dot{V}O_2$ -maximum rate of oxygen, W_{max}- maximum workload

RESULTS

3.1 Meta-analysis: The meta-analysis included 18 studies (248 participants) that fulfilled the inclusion criteria. (Fig 1) depicts the study selection flowchart. All included research was in reputed journals. Pooled prevalence- 18 studies reported the pre-exercise levels of I-FABP and post-exercise changes in the I-FABP. The pooled mean difference (increase) post-exercise is 488.36 [95% CI: 280.35 – 696.37] (Fig. 2). The drapery plot (Supplementary S2; Fig 1) depicts that the pooled estimate remains significant even at $p < 0.001$. Heterogeneity - The individual study estimates showed substantial heterogeneity with an I^2 of 94%, and a significant Cochran's Q ($p < 0.01$). The prediction interval of -427.52 to 1404.24 shows that a similar original study in the future is expected to give a result (mean difference) in this range. No subgroup analysis or meta-regression has been performed to reduce this heterogeneity, as no suitable variable was found. Sensitivity analysis- We performed a sensitivity analysis, omitting each study individually (Supplementary S2; Fig 2). The findings are robust and did not become insignificant with the omission of any study.

I-FABP variations 1-hour post-exercise: Eight studies reported the 1-hour I-FABP values post-exercise (Fig 4a). The shrinkage in pooled mean difference −291.38 [95% CI: −525.22; −57.53] depicts the de-escalation of I-FABP value at resting state after exercise. With 86% I^2, considerable heterogeneity among the selected studies was detected at a significant Cochrane's Q ($p < 0.01$).

I-FABP variations 2-hour post-exercise**:** Among the selected studies, 8 reported the 2-hour post-exercise I-FABP level with a negative pooled estimate of −188.00 [95% CI: −461.31; 85.31] (Fig 4b), suggesting a lowering in the value of I-FABP. An I^2 of 86% with substantial heterogeneity was observed at Cochrane's Q ($p < 0.01$).

I-FABP variations 4-hour post-exercise: Six studies with a pooled estimate of −530.05 [95% CI: −840.83; −219.28] (Fig 4c) and heterogeneity with 87% I^2 reported a decline in the I-FABP level 4-hour post-exercise.

3.2 ROB assessment: Certain studies were rated as having 'some concerns' in specific categories because they did not explicitly disclose their blinding and randomization processes or because it was not feasible to completely blind participants or researchers. Ative period and carryover effects, impacts of intervention adherence, and outcome assessment; however, most of the included studies had a low overall risk of bias because the number of researchers used a randomized crossover approach (Fig 2). The overall risk of bias is low for most studies (Supplementary S1; Table 2).

Figure 2 Rob assessment summary using the Cochrane tool for all the included studies

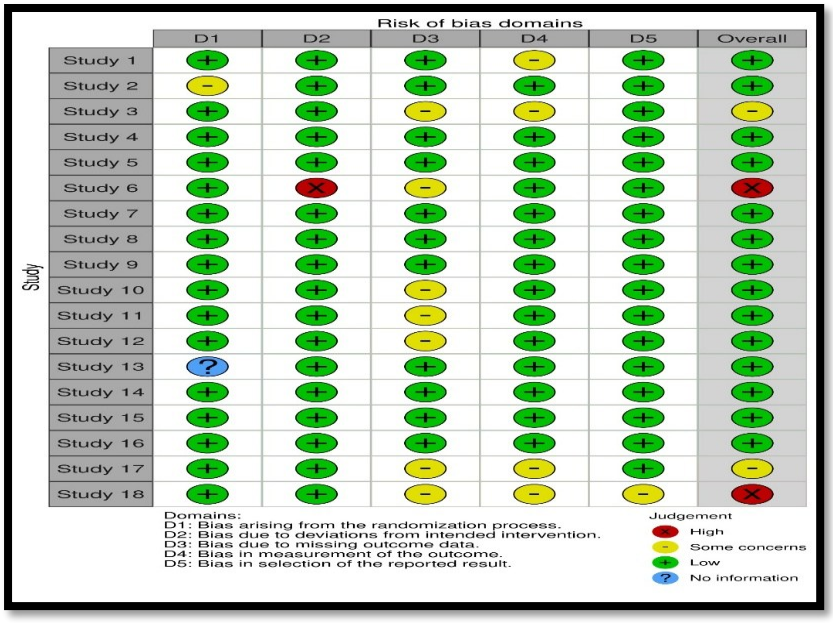


Figure 3 Forest plot for studies comparing I-FABP before and after exercise sessions

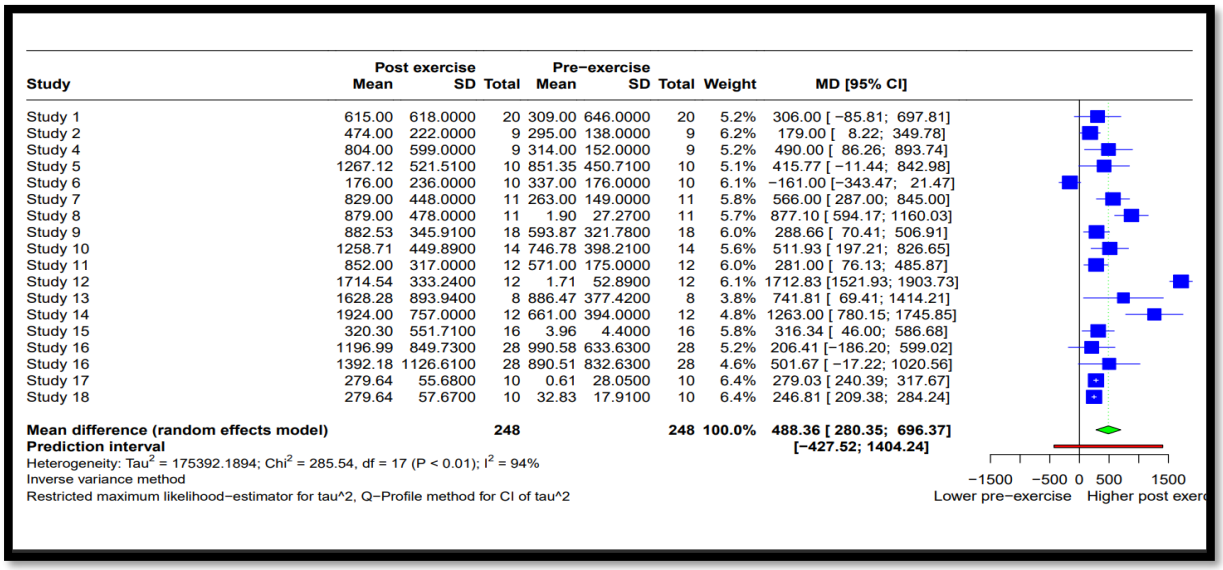
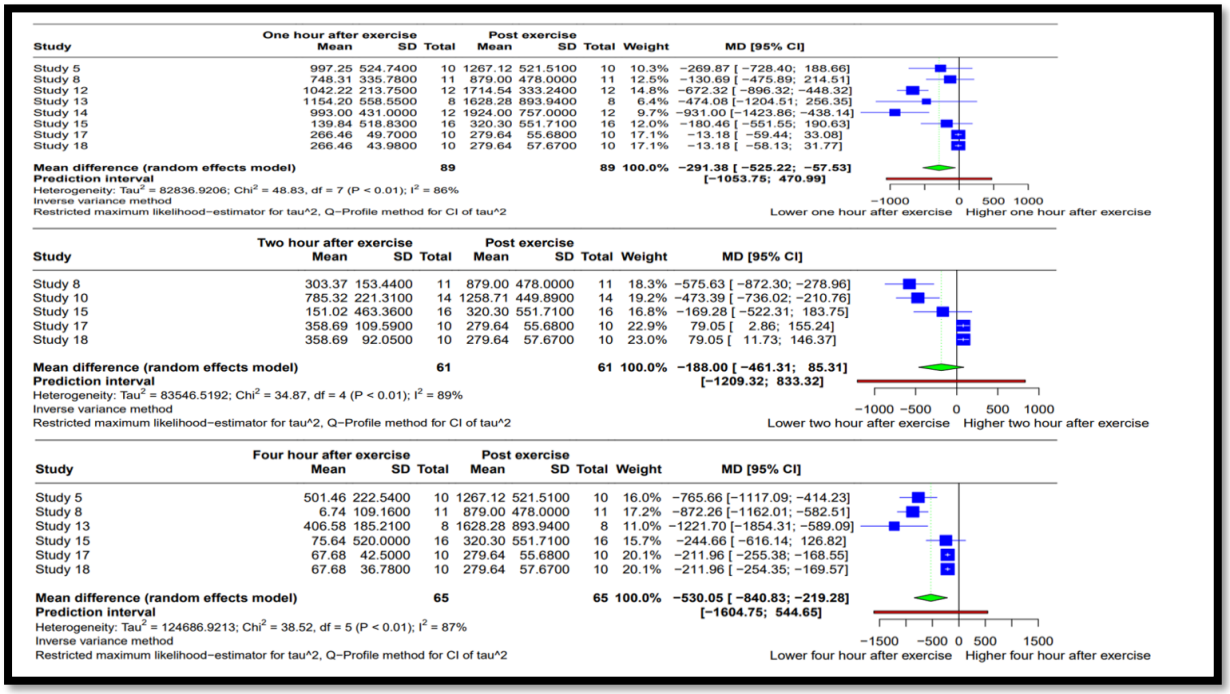


Fig 4. (a) Forest plot for studies estimating the impact of the 1-hour post-exercise session of I-FABP
(b) Forest plot for studies estimating the impact of the 2-hour post-exercise session of I-FABP
(c) Forest plot estimating the impact of the 4-hour post-exercise session of I-FABP



3.3 Publication Bias: For assessing publication bias and small-study effects, we used both a trim-and-fill contour-enhanced funnel plot (Supplementary S2; Fig 3) and a Doi plot (Supplementary S2; Fig 4). The funnel plot shows visible asymmetry, with several studies imputed chiefly at the mean and negative mean-difference levels. The grossly asymmetrical Doi plot also indicates potential publication bias. A quantitative interpretation in the form of an LFK index of 3.74 corroborates this (Supplementary S2; Fig 4).

DISCUSSION

The objective of this meta-analysis was to look at the influence of a deep workout routine on indicators of gut injury and cell damage and the role of moderators such as exercise periods at

ambient temperature. Synthesis of enterocyte-derived intestinal fatty-acid binding protein (I-FABP) is believed to be encouraged by strenuous workouts, which is an intestinal enterocyte damage and ischemia biomarker. Post extended exercises (≥1 h) and resistance drills of shorter duration (30 min), the augmented release of I-FABP is observed into circulation, which specifies damage to mature enterocytes (35). Since the injured mucosa of the intestine releases I-FABP into the circulation, a rise in serum levels indicates more excellent intestinal permeability (36, 37).

The association of I-FABP is certified with splanchnic hypo-perfusion linked to exercise and subsequent ischemia (38). In this study, I-FABP was determined before the beginning of the trial and after the workout. The post values point to a reasonable increase in its value, depicting significant injury to the epithelial cells of the intestine. Similar results have been reported, where 17 participants ran 90 minutes with 80% of their finest effort and raced at a speed of 10 km (39). The increased I-FABP levels are a significant challenge to other investigations in endurance sportspersons (40).

The studies in the analysis outline that the exercise trial lasts 20 minutes or more than that, likely to encourage splanchnic hypoxia. The studies have reported significant gut damage when the temperature exceeded 22°C (27, 32, 34). Sixty minutes of exercise trial depicts elevation in the I-FABP level; running with 70% $V\dot{O}_2$ peak at 30°C (21, 28), 65% maximum $V\dot{O}_2$ (28), and cycling with 70% maximum workload (18).

The level of I-FABP was observed to decline to the starting point values, followed by 2 to 4 hours of completing the exercise. Post 1-hour exercise, I-FABP concentration in volunteers had a lower trend than immediately after exercise (21, 24, 28, 30). These results indicate that resting normalizes exercise-induced epithelial cell damage. A similar trend was seen at lowered 2-hour and 4-hour post-exercise I-FABP values (21, 24, 31).

It was anticipated that a rise in I-FABP levels would accompany alterations in permeability. Overall, we found a significant and modest effect size for upsurges in injury and permeability of the gut by measuring I-FABP against a session of exercise in the 17 included trials (17, 18, 20, 21, 23-25, 27-34, 41). Thus, displaying I-FABP after vigorous exercise can be a sensitive and rapid indicator of intestinal cellular damage.

I-FABP levels rise right after exercise and return to normal within hours, making it a sensitive and quick indicator of intestinal damage brought on by exercise, according to this meta-analysis. However, generalisability is constrained by the lack of standardised cut-off values, notable study heterogeneity, and differences in measurement techniques. Notwithstanding these limitations, the results demonstrate that intense exercise temporarily impairs the integrity of the gut barrier, with I-FABP acting as a trustworthy marker. The study advances our understanding by highlighting the importance of exercise duration, intensity, and environmental stress as major determinants of gastrointestinal damage. This information is useful for sports medicine and athlete health monitoring.

CONCLUSION

According to this meta-analysis, a consistent mean increases in I-FABP across studies conducted over the past ten years indicates that even one intense exercise session can seriously harm the intestinal epithelium in healthy people. The results directly meet the stated goals, which were to measure the impact of exercise on gut permeability and epithelial damage in normotensive individuals who were not taking supplements.

The study fills a significant gap in sports medicine for athletes and trainers by validating I-FABP as an objective marker for the quick evaluation of exercise-induced GI barrier compromise. The results' generalisability is, however, constrained by the notable heterogeneity among the included studies (differences in exercise regimens, temperature, measurement methods, and demographics).

A deeper understanding of moderating variables like age, gender, or type of exercise is hindered by the lack of subgroup and meta-regression analyses, caused by data

limitations. Furthermore, no research has documented long-term, chronic GI effects or repercussions for populations with underlying intestinal disorders.

Recommendation

The recommendation area of this project can be summarized as:

Promoting standardized exercise protocols, nutritional and hydration strategies, and environmental considerations to minimize exercise-induced gut injury and support gastrointestinal health in active individuals.

Limitation of the Study

The findings are limited by significant variability in study design, participant demographics, exercise protocols, and measurement methods, as well as the absence of analyses exploring moderators like age or exercise type; additionally, the results pertain only to healthy participants and may be affected by possible publication bias and small-study effects.

Relevance of the Study

- I-FABP fluctuations as a marker for gut injury during and at predetermined intervals following intense exercise in a placebo-controlled setting are systematically meta-analyzed for the first time in this review.
- This confirms the usefulness of I-FABP as a quick, sensitive, and non-invasive biomarker for identifying intestinal epithelial compromise brought on by exercise. This biomarker is crucial for sports medicine, GI physiology research, and public health initiatives aimed at improving the health of athletes.
- This emphasises how important it is to take environmental stress, hydration, and recovery techniques into account when creating athlete training and safety procedures.

Authors Contribution

NR and MAK perceived and planned the review. NR steered the literature searches. NR and MAK marked off the titles, mined data individually, and evaluated the full-text articles. NR performed the quality valuation of the suitable studies. MAS performed the statistical analysis and contributed to edging results with NR. NR wrote the manuscript; AP reviewed the manuscript. All the authors read and approved the final manuscript.

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Conflict of Interest

There are no conflicts of interest.

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Declaration Of Generative AI And AI Assisted Technologies In The Writing Process

This manuscript was prepared and written entirely by the authors without the use of generative AI or AI-assisted technologies.

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