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Exercise-induced METRNL responses may depend on inflammatory and physiological context

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Abstract

Objective

Variable findings regarding exercise-induced Meteorin-like protein (METRNL) responses in the literature suggest that this biomarker may be associated not only with exercise modality or intensity, but also with the physiological conditions accompanying exercise exposure. This exploratory study aimed to evaluate exercise-related METRNL response patterns and to investigate potential associations between METRNL response direction and exercise modality, exercise intensity, sampling time, fasting status, and inflammation-related study findings.

Methods

Studies investigating exercise-related METRNL responses were identified through searches conducted in the PubMed, Scopus, and Web of Science databases. METRNL response direction following exercise interventions was categorized as increase, no change, or decrease. Exercise modality, exercise intensity, sampling time, fasting status, and inflammation-related study findings were evaluated within the scope of exploratory categorical analyses. Associations between categorical variables were analyzed using the Pearson chi-square test.

Results

A total of 35 exercise-related observations were evaluated, and sufficient data to classify METRNL response direction were available in 26 observations. Most observations reported increased METRNL levels following exercise interventions (80.8%). No significant associations were observed between METRNL response direction and exercise modality ($p = 0.513$), exercise intensity ($p = 0.783$), sampling time ($p = 0.348$), or fasting status ($p = 0.201$). In contrast, a significant association was identified between inflammation-related study findings and METRNL response direction ($\chi^2=18.652$, $p < 0.001$). Increased METRNL responses were more frequently observed in inflammation-related observations.

Conclusion

The findings suggest that exercise-induced METRNL responses may not be explained solely by exercise characteristics and may need to be interpreted together with the biological context accompanying exercise exposure. In addition, METRNL response patterns may vary depending on the physiological conditions under which exercise occurs. Nevertheless, the present findings should be interpreted as hypothesis-generating exploratory observations due to the methodological heterogeneity and limited number of available observations.

Highlights

• Most studies reported an increase in METRNL levels following exercise interventions.

• No clear association was observed between METRNL response direction and exercise modality or exercise intensity.

• Increased METRNL responses were more commonly observed in observations classified as inflammation-related.

• METRNL response patterns appeared to vary according to inflammation-related and physiological context rather than exercise characteristics alone.

• The findings support a context-dependent interpretation of exercise-induced METRNL responses.

INTRODUCTION

Due to its regulatory effects on metabolic and immune system functions, exercise has attracted increasing attention for its importance in the prevention and treatment of globally prevalent metabolic and neurological diseases. In maintaining healthy physiological functions throughout life, a wide variety of signaling molecules released from skeletal muscle contribute to the bidirectional interaction between exercise and the immune system. Because exercise exerts regulatory effects across multiple biological systems, various exerkines are released as mediators of interorgan communication during this process. In recent years, exerkines have been suggested to contribute not only to local muscle-specific responses, but also to multidirectional biological communication among metabolic, immunological, and neurological systems, thereby participating in physiological adaptation processes associated with exercise. Within this framework, myokines released from skeletal muscle are considered important regulators of exercise-induced biological responses (Chow et al., 2022; Martínez-Gayo et al., 2025; Zaccardi et al., 2025).

Meteorin-like protein (METRNL), also known as Subfatin or Cometin, is a myokine that has attracted attention because of its anti-inflammatory and metabolic properties. Although METRNL is primarily secreted from skeletal muscle and adipose tissue, unlike classical adipokines, it does not directly target adipocytes, which has further increased interest in its potential roles in immunometabolism and muscle regeneration (Rao et al., 2014; Baht et al., 2020; Miao et al., 2020; Bilski et al., 2022; Li et al., 2023; Marmondi et al., 2025).

Nevertheless, findings regarding exercise-induced METRNL responses are not entirely consistent across the literature. While several studies have reported increased METRNL levels following acute or chronic exercise, other studies have demonstrated minimal alterations or variable responses depending on physiological conditions (Jamrasi et al., 2025; Oskay et al., 2025; Zhou et al., 2026). These findings suggest that METRNL responses may not be explained solely by exercise modality or intensity, but may also need to be interpreted together with the inflammatory and metabolic context accompanying exercise exposure.

Therefore, the present exploratory study aimed to evaluate exercise-related METRNL response patterns reported in the literature and to investigate potential associations between METRNL response direction and exercise modality, exercise intensity, sampling time, fasting status, and inflammation-related study findings. In addition, this study aimed to explore whether inflammatory and physiological context may contribute to the variability of exercise-induced METRNL responses.

METHODS

Literature Search and Study Selection

Studies investigating exercise-related METRNL responses were identified through literature screening of published articles. To increase the transparency of the study selection process, elements of the PRISMA statement were considered where applicable to the exploratory design of this study. Literature searches were conducted in PubMed, Scopus, and Web of Science using the keywords “METRNL”, “meteorin-like”, “meteorin like”, and “subfatin”. A total of 1,052 records were identified. After removal of 592 duplicate records, 460 records remained for screening. Titles, abstracts, and full texts were screened for relevance to exercise-related METRNL outcomes. The remaining records were then assessed for eligibility based on their relevance to exercise-related METRNL outcomes, and 21 studies were included in the final exploratory analysis. Original research articles examining acute or chronic exercise interventions and reporting METRNL-related outcomes were evaluated for eligibility. Because some included studies reported multiple exercise conditions, sampling points, or intervention arms, study-level records were further separated into exercise-related observations where appropriate. Accordingly, 35 exercise-related observations were extracted from the 21 included studies, and 26 observations provided sufficient information to classify METRNL response direction. A PRISMA-based flow diagram illustrating the study identification and selection process is presented in Supplementary Fig. 1. Studies without exercise-related METRNL findings, review articles, editorials, conference abstracts, and studies lacking sufficient information for categorical classification were excluded from the analyses.

When multiple exercise conditions or sampling points were reported within the same study, these observations were evaluated separately when appropriate for categorical assessment. Fasting status was categorized based on the information provided in the original studies as fasting, non-fasting, short-term fasting, or unspecified when sufficient methodological details were unavailable. Because the aim of the present study was exploratory categorization rather than quantitative evidence synthesis, no pooled effect-size calculations or meta-analytic procedures were performed.

Data Extraction and Coding Strategy

Studies examining exercise-related METRNL responses were reviewed in detail, and relevant data were extracted manually from the original articles. The extracted variables included exercise modality, exercise intensity, sampling time, fasting status, and the reported direction of METRNL response following exercise interventions.

For categorical analyses, METRNL responses were classified as “increase,” “no change,” or “decrease” according to the results reported in the original studies. In studies where fully extractable numerical data were not available, classifications were based on the direction of change described by the study authors.

Inflammation-related coding was performed when inflammatory markers, cytokine responses, or inflammation-associated pathways were directly evaluated or discussed together with METRNL findings in the original study. This classification was used to explore potential relationships between inflammation-related findings and METRNL response patterns across different exercise conditions.

Reporting methods and outcome presentation varied substantially across studies; therefore, the analyses were interpreted as exploratory.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (Version 27.0; IBM Corp., Armonk, NY, USA). Due to the methodological variability among the included studies, the analyses were planned as exploratory categorical evaluations rather than pooled quantitative effect-size analyses. METRNL responses reported in the original studies were classified into three categories: increase, no change, or decrease following exercise interventions.

Associations between METRNL response direction and exercise-related variables, including exercise modality, exercise intensity, sampling time, fasting status, and inflammation-related study coding, were evaluated using Pearson's chi-square test. Exercise intensity categories were grouped according to the classifications reported in the original studies.

Categorical data were presented as frequencies and percentages. Statistical significance was accepted at $p < 0.05$. Since some subgroup categories contained a limited number of observations, the findings were interpreted cautiously and considered exploratory rather than definitive.

RESULTS

A total of 35 exercise-related observations were screened, and 26 of them contained enough information to classify the direction of the METRNL response (Table 1). In most observations, METRNL levels increased after exercise (80.8%) (Fig. 1). No change was reported in 15.4% of cases, while a decrease was observed in only one cold-water exercise condition (3.8%) (Fig. 1).

Table 1
Characteristics of exercise-related METRNL observations included in the exploratory dataset

Variable	Category	n (%)
Exercise type	Aerobic	13 (43.3)
	Resistance	3 (10.0)
	Combined	7 (23.3)
	HIIT	7 (23.3)
Exercise intensity	Moderate	18 (64.3)
	High	10 (35.7)
Sample timing	Acute/session	2 (6.5)
	Hours	5 (16.1)
	Short-term	2 (6.5)
	Weeks	10 (32.3)
	Chronic	12 (38.7)
METRNL response	Increase	21 (80.8)
	No change	4 (15.4)
	Decrease	1 (3.8)
Inflammation status	Present	25 (80.6)
	Absent	6 (19.4)

The bar graph presents the distribution of observations according to the direction of METRNL response following exercise interventions. Most observations demonstrated an increase in METRNL levels (21/26, 80.8%), whereas unchanged responses (4/26, 15.4%) and decreased responses (1/26, 3.8%) were observed less frequently. Overall, increased METRNL responses were the most common finding across the included observations.

Associations between METRNL response direction and exercise-related variables were evaluated using exploratory categorical analyses. No significant associations were observed between METRNL response direction and exercise modality (χ^2=5.247, p = 0.513), exercise intensity (χ^2=0.490, p = 0.783), sampling time (χ^2=6.719, p = 0.348), or fasting status (χ^2=5.970, p = 0.201) (Table 2).

Table 2
Associations between METRNL response direction and exercise-related variables.

Variable	χ^2	df p value
Exercise modality	5.247 6	0.513
Exercise intensity	0.490 2	0.783
Sample timing	6.719 6	0.348
Fasting status	5.970 4	0.201
Inflammation-related coding	18.652 2	< 0.001*

**Statistically significant association.*

However, a different pattern was observed for inflammation-related study coding. A significant association was detected between inflammation-related coding and METRNL response direction (χ^2=18.652, $p < 0.001$). Increased METRNL responses were observed more frequently in inflammation-related observations, whereas observations without inflammation-related findings were more commonly associated with stable METRNL levels (Fig. 2).

The clustered bar graph illustrates the distribution of inflammation-related and non-inflammation-related observations across METRNL response categories. Increased METRNL responses were more frequently observed in inflammation-related observations, whereas observations without inflammation-related findings were more commonly represented within the no-change category. This visual distribution was consistent with the significant association observed in the categorical analyses ($\chi^2 = 18.652$, $p < 0.001$).

Because some subgroup categories included relatively few observations, these analyses should be considered exploratory. Overall, METRNL responses appeared to vary more prominently according to inflammation-related and physiological context than exercise methodology alone.

DISCUSSION

In the present exploratory analysis, increased METRNL responses represented the most frequently observed finding across exercise-related observations. However, no significant associations were detected between the direction of METRNL response and exercise modality, exercise intensity, sampling time, or fasting status. In contrast, increased METRNL responses appeared to occur more frequently in studies involving inflammation-related findings. Taken together, these observations suggest that exercise-related METRNL responses may not be explained solely by the mechanical or structural characteristics of exercise, but may also be influenced by the accompanying physiological and inflammatory context.

The inflammation-related classification used in the present study was not intended as a standardized clinical or diagnostic categorization. Instead, it was designed as an exploratory contextual coding approach to determine whether inflammatory processes, cytokine responses, or inflammation-associated mechanisms were evaluated together with METRNL findings in the original studies. The current findings do not suggest that exercise modality itself is biologically irrelevant. Rather, exercise-induced METRNL responses may be substantially influenced by inflammatory, metabolic, and physiological context. In this framework, METRNL responses may appear to be more context-sensitive than uniformly exercise-responsive across different physiological conditions.

To date, numerous studies have demonstrated that exercise contributes to improvements in cardiovascular, metabolic, neurological, and psychological disorders. Through its effects on metabolic homeostasis, physical activity may alter immune cell phenotypes and influence immunological plasticity (Nieman and Wentz, 2019; Severinsen and Pedersen, 2020; Rosa-Neto et al., 2022; Callegari et al., 2023). More recently, the emerging concept of immunometabolism has proposed that exercise-induced metabolic alterations may reshape the functional characteristics of immune cells and contribute to inflammatory adaptation (Severinsen and Pedersen, 2020; Rosa-Neto et al., 2022; Callegari et al., 2023).

The beneficial effects of exercise are no longer considered to be restricted solely to skeletal muscle. Instead, exercise appears to promote an integrated communication network involving adipose tissue, liver, brain, and immune-related systems (Severinsen and Pedersen, 2020; Chen et al., 2022). Within this communication network, myokines have been proposed as key signaling mediators (Fuentes-Barría, 2025). The fact that myokines may be secreted not only from skeletal muscle, but also from adipose tissue, brain, intestine, bone, and immune cells suggests that myokine responses may be highly variable and context-dependent (Pedersen, 2019; Severinsen and Pedersen, 2020; Dong et al., 2024; Velikova et al., 2025). Accordingly, exercise-induced myokine responses may be associated not only with exercise modality or intensity, but also with inflammatory and metabolic conditions.

When considered specifically in the context of exercise physiology, different exercise modalities and recruitment of distinct muscle groups may induce variable myokine responses, and some myokines may even exert central effects after crossing the blood-brain barrier (Kostka et al., 2024; Dai et al., 2025; Velikova et al., 2025; Zhou et al., 2026). High-intensity and resistance-based exercise protocols, in particular, have been reported to induce more pronounced myokine responses. Within this framework, METRNL, which has emerged as an exercise-responsive myokine, may be associated not only with energy metabolism but also with inflammatory and immune-related processes. Experimental evidence suggests that METRNL may support alternative macrophage activation and participate in immune-metabolic interactions associated with energy homeostasis (Rao et al., 2014). Acute exercise has been associated with anti-inflammatory actions of METRNL and improvements in insulin sensitivity, whereas obesity and chronic inflammatory conditions have been linked to distinct inflammatory response patterns involving METRNL (Benatti and Pedersen, 2015; Severinsen and Pedersen, 2020; Dong et al., 2024; Alizadeh et al., 2025; Shero et al., 2025). Collectively, these findings suggest that METRNL responses may vary according to the metabolic and inflammatory conditions accompanying exercise. In

addition, METRNL responses may vary during physiological adaptations associated with exercise exposure.

A 12-week exercise intervention conducted in older adults reported associations between circulating METRNL changes and inflammatory markers, physical performance, and cognitive function (Jamrasi et al., 2025). Similarly, experimental swimming models suggested that METRNL responses may vary during adaptation to repeated exercise exposure (Oskay et al., 2025). Furthermore, several studies have reported positive associations between circulating METRNL levels and increased physical activity (Jamrasi et al., 2025; Li et al., 2025; Li et al., 2026; Kaya et al., 2026).

Recent advances in multi-omics technologies indicate that circulating and exosomal exercise-responsive biomarkers may contribute not only to metabolic regulation but also to inflammatory adaptation (Ahima and Lazar, 2008; Khoramipour et al., 2025). These developments have also facilitated the identification of novel molecular markers in exercise physiology. However, the relevance of a biomarker may depend not only on its identification, but also on understanding where, when, and to what extent it changes under acute and chronic exercise conditions. This may partly explain why no significant association was observed between METRNL responses and exercise modality or intensity in the present study, whereas METRNL increases appeared to be more common in inflammation-related observations. Similarly, the heterogeneous nature of exercise-induced biomarker responses across studies suggests that biological adaptation processes may not be explained solely by exercise protocols alone (Marmondi et al., 2025). Biological signaling may be shaped by multiple factors, including sampling time, previous exercise load, recovery status, and metabolic environment (Nieman et al., 2018; Merritt et al., 2019; Mănescu et al., 2026). Recent systems-based exercise biomarker models suggest that interpretation of biological adaptation may require integrated evaluation of multiple physiological signals rather than reliance on a single circulating biomarker alone (Mănescu et al., 2026). Therefore, METRNL responses may reflect context-dependent physiological adaptations associated with inflammatory and metabolic conditions accompanying exercise.

Several limitations of this study should be acknowledged. First, the analyses were based on a limited number of exercise-related observations obtained from methodologically heterogeneous studies. The relatively small number of observations in certain subgroups limits the interpretation of findings related to exercise modality, exercise intensity, sampling time, and fasting status as definitive conclusions. In addition, because fully extractable numerical pre-post data were not available in all studies, some observations were classified according to the direction of response reported by the original authors. The inflammation-related coding approach was not designed as a standardized clinical classification, but rather as an exploratory contextual categorization based on whether inflammatory markers, cytokine responses, or inflammation-associated mechanisms were evaluated together with METRNL findings in the original studies. Accordingly, the present findings should be interpreted as hypothesis-generating observations suggesting that exercise-induced METRNL responses may vary according to biological context rather than as evidence of a direct causal relationship.

Based on the present findings, sportomics-oriented approaches integrating inflammatory burden together with metabolic and endocrine characteristics may contribute to a more comprehensive interpretation of exercise-responsive adipokines, including METRNL. Large-scale longitudinal cohort studies may further clarify the potential role of METRNL within the broader concept of “metabolic fitness.” In this context, recently proposed sportomics, enduromics, and resistomics frameworks aim to evaluate molecular responses to exercise at the individual level and facilitate the development of biomarker-guided personalized exercise strategies (Khoramipour et al., 2025).

DECLARATIONS

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data analysed during this study are included in this published article. No new datasets were generated during the current study.

Authors' contributions

KE conceived the study, performed the literature search, extracted and coded the data, conducted the statistical analyses, interpreted the findings, and drafted the manuscript. GG contributed to study design, interpretation of the findings, and critical revision of the manuscript. EK contributed to data extraction, data verification, and manuscript revision. All authors read and approved the final manuscript.

Competing interests

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The authors declare that they have no competing interests.

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Figures

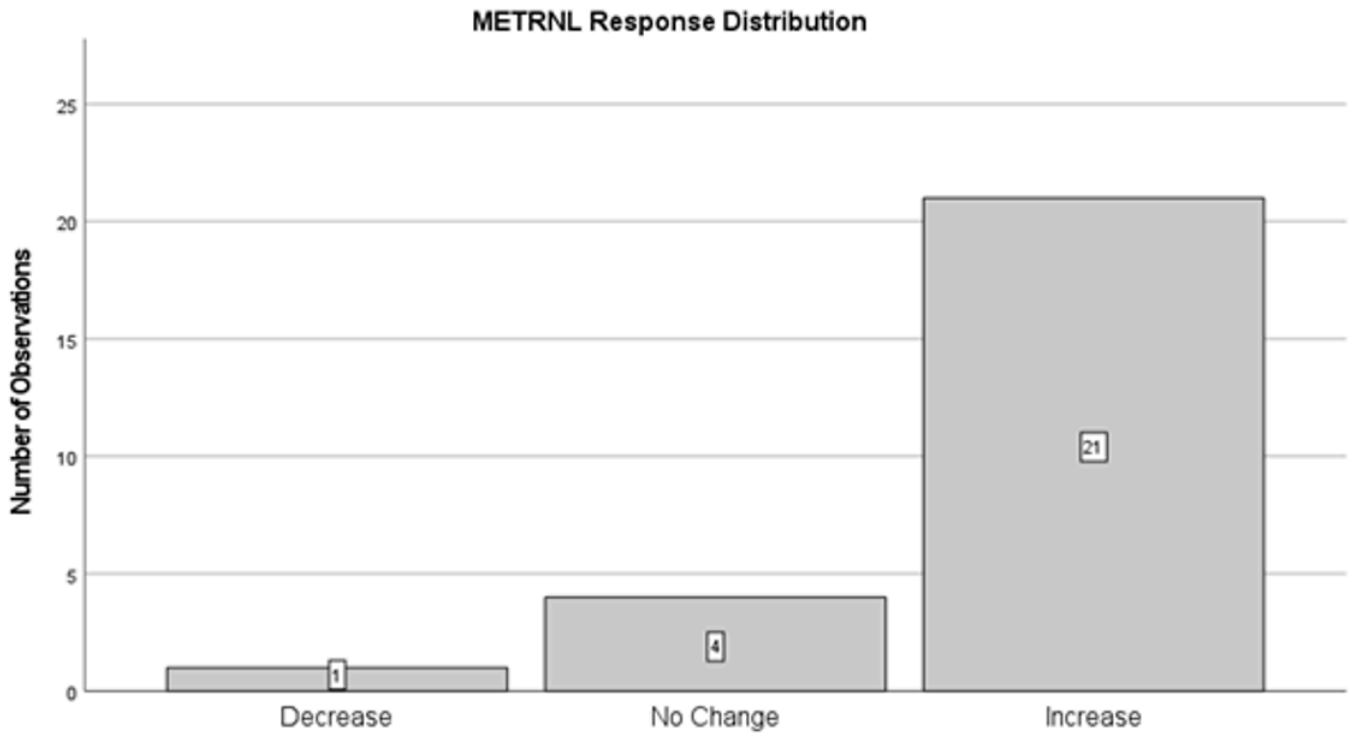


Figure 1

Distribution of METRNL response direction across exercise-related observations

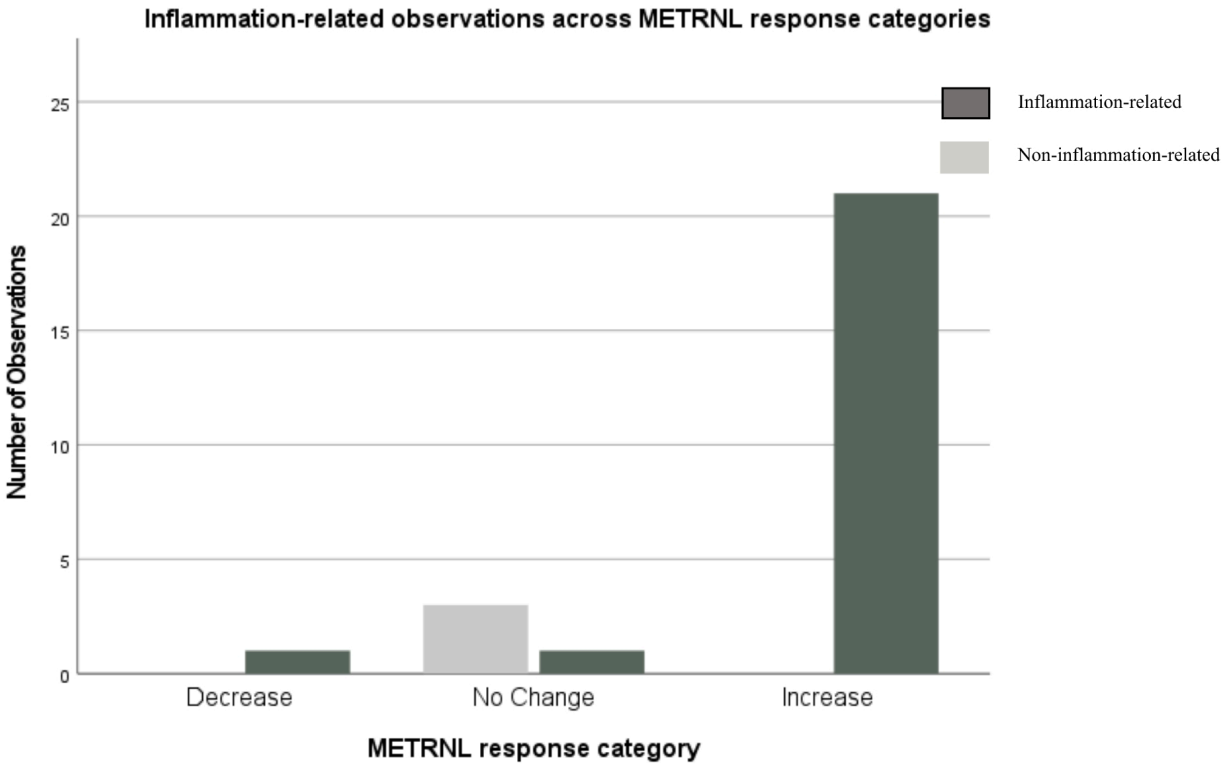


Figure 2

Distribution of inflammation-related and non-inflammation-related observations across METRNL response categories.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile2PRISMAFlowDiagramd1.pdf