Dose–Response Effects of Prescribed Physical Exercise on Immune Function and Health Outcomes: A Systematic Review and Meta-Analysis

Alvino Ramadhany Putra, Moch. Yunus*, Nanang Tri Wahyudi, Faiz Apta Zufartsany, and Izzah Fadhilah Robbani

Department of Medicine, Faculty of Medicine, Universitas Negeri Malang, Malang, Indonesia
moch.yunus.fk@um.ac.id

Abstract. Background: Physical exercise is widely recognized as a potent non-pharmacological strategy that yields substantial immunological and clinical benefits. However, conventional literature frequently relies on binary comparisons (active versus inactive), thereby limiting the mechanistic understanding of the optimal exercise "dosage" required for precise immunomodulation. **Objective:** This systematic review and meta-analysis evaluated the quantitative dose–response relationship between structured physical exercise, adaptive immune responses, and clinical health outcomes. **Methods:** Following the PRISMA guidelines, a systematic literature search was conducted across PubMed, Scopus, and Web of Science up to February 2026. Eligible studies comprised randomized controlled trials (RCTs) and controlled clinical interventions that specified explicit exercise dose parameters (intensity, frequency, duration, modality) and quantified measurable immunological or clinical endpoints. Data synthesis was performed utilizing a random-effects model alongside dose–response and subgroup analyses. **Results:** Twenty-one studies fulfilled the rigorous inclusion criteria. Prescribed physical exercise performed at moderate-to-high intensities significantly enhanced immune function, characterized by elevated natural killer (NK) cell cytotoxic activity, robust T- and B-cell proliferation, and an optimized pro- versus anti-inflammatory cytokine balance. These cellular adaptations directly correlated with diminished systemic inflammation, enhanced metabolic homeostasis, and superior quality-of-life indices. Dose–response mathematical modeling unveiled a distinctive non-linear (U-or J-shaped) relationship. Optimal immunotherapeutic efficacy was clustered at 30–60 minutes per session, at least three times per week, at an intensity of ≥ 60% of maximum oxygen uptake (VO2max). Conversely, exhaustive exercise configurations approaching or exceeding 90% VO2max triggered transient adverse systemic inflammatory spikes. **Conclusion & Clinical Implications:** Structured physical exercise exhibits a quantifiable dose–response profile on immune and clinical outcomes, validating its clinical implementation as a viable non-pharmacological immunotherapy. These findings provide an empirical foundation for precision exercise prescriptions within preventative medicine and clinical rehabilitation frameworks.

Keywords: Exercise prescription, Dose–response, Immune function, Health outcomes, Nonpharmacological immunotherapy.

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K. M. Ariesaka and D. Fauziah (eds.), *Proceedings of the 3rd Malang International Conference on Medical and Health Sciences (MICROMEDHS 2026)*, Advances in Health Sciences Research 96,
https://doi.org/10.2991/978-94-6239-807-8_17

1 Introduction

Physical exercise has long been recognized as having significant immunological effects. Structured physical activity not only improves cardiometabolic capacity but also modulates immune system responses, including immune cell mobilization, cytokine regulation, and reductions in systemic inflammatory markers (Huang et al., 2025). In the era of chronic disease prevention, non-pharmacological interventions such as exercise have become increasingly important because they can reduce the risk of inflammatory, metabolic, and cardiovascular diseases through measurable biological mechanisms (Xiang & Su, 2025). Most previous literature has compared "active" and "inactive" groups without considering the quantitative dosage of exercise. This limitation reduces the ability to determine optimal exercise prescriptions for improving immune function and clinical outcomes. Therefore, this study emphasizes the dose-response relationship between structured exercise, immune adaptation, and clinical benefits.

The main independent variable in this study is the dose of structured physical exercise, which includes several key components, namely exercise intensity (%HRmax, %VO_2max), frequency (sessions per week), duration (minutes per session), cumulative weekly volume, and type of exercise such as aerobic, resistance, or combined training. These parameters allow exercise to be viewed as a measurable therapeutic exposure rather than merely random physical activity. Through this approach, exercise dose can be analyzed quantitatively to identify the optimal threshold for immune system modulation. Previous studies have shown that exercise performed at moderate to high intensity over several weeks can increase natural killer cell mobilization, enhance the proliferation of T and B cells, and balance the ratio of pro- and anti-inflammatory cytokines (Shi et al., 2025). This finding highlights the need for a prescriptive exercise approach that considers measurable dosage, frequency, and duration to achieve maximal immune benefits.

The mediator variable in this model is the immunological adaptation that occurs in response to structured exercise. Commonly analyzed parameters include immune cells such as natural killer cells, T cells, and B cells, inflammatory cytokines such as IL-6, TNF-α, and IL-10, as well as systemic inflammatory markers such as C-reactive protein (Menzel et al., 2021). These immune adaptations represent the biological mechanisms that connect exercise stimulus with clinical outcomes. For example, increases in natural killer cells and IL-10 are associated with reductions in chronic inflammation and improvements in metabolic function. By examining these mediator variables, the study can assess how different exercise doses trigger specific immune responses, which subsequently influence clinical health outcomes.

The main dependent variable is the tangible health benefit that arises from immune modulation. The clinical outcomes analyzed include reductions in chronic inflammation, improvements in metabolic function, enhanced quality of life, and improved cardiometabolic function. Dose-response analysis enables this study to

connect the magnitude of immune changes with the magnitude of clinical changes, providing direct evidence that exercise prescription can be applied therapeutically (Bettariga et al., 2025).

Studies involving both healthy populations and patients with chronic diseases demonstrate that structured exercise can reduce C-reactive protein levels, improve T and B cell responses, and increase endogenous antioxidant activity (Makiel et al., 2025). These findings confirm the clinical role of exercise as a measurable non-pharmacological strategy, allowing it to be incorporated into evidence-based health guidelines (Ferreira et al., 2024). Although many studies confirm the immune benefits of physical activity, few studies quantitatively link structured exercise dosage, immune adaptation, and clinical outcomes. The novelty of this research lies in clarifying the quantitative relationship between exercise dose and immune modulation, reframing exercise as a non-pharmacological immunotherapy rather than merely a preventive activity, integrating immune biomarkers with health outcomes to provide a translational physiology model that connects stimulus, biological mechanisms, and clinical outcomes, and providing a quantitative synthesis across populations and study designs that enables the identification of optimal exercise doses for different groups of individuals. Within this framework, this systematic review and meta-analysis seeks to provide high-level scientific evidence supporting exercise as prescriptive medicine and as a measurable immunotherapeutic strategy.

2 Methods

2.1 Study Design

This study employed a systematic review and meta-analysis following the PRISMA guidelines. This approach enables a quantitative synthesis of literature evaluating the relationship between the dose of structured physical exercise, immune adaptation, and clinical outcomes. Dose-response analysis was conducted using both linear and non-linear models to evaluate whether there is a threshold or optimal range of structured exercise that produces the most significant immune modulation.

2.2 Inclusion Criteria

The inclusion criteria were determined to ensure that the analyzed studies were relevant to the objectives of the research. Eligible studies included randomized controlled trials or controlled intervention studies involving adult or older populations who were either healthy or had chronic diseases, such as obesity or inflammatory conditions. The interventions had to involve structured physical exercise with clearly defined dose parameters, including exercise intensity expressed as %HRmax or %VO_2max, frequency measured as sessions per week, duration measured in minutes per session, and the type of exercise such as aerobic, resistance, or combined training. The primary outcomes included immune biomarkers such as natural killer cells, T cells, B cells, pro- and anti-inflammatory cytokines, and C-reactive protein. Secondary outcomes included

health outcomes such as metabolic function, chronic inflammation, quality of life, and cardiometabolic function. Only articles published in Indonesian or English between 2016 and 2026 were included in the analysis. Studies meeting these criteria included aerobic, resistance, and combined exercise interventions reported in previous research such as Bartlett et al. (2018), Tenório et al. (2018), and Gerosa-Neto et al. (2020), in which exercise dose, duration, and intensity were recorded in measurable terms.

2.3 Exclusion Criteria

Studies were excluded if they did not meet the methodological or conceptual requirements of this research. Observational studies without measurable exercise dosage were excluded because they do not allow dose-response analysis. Studies focusing exclusively on HIV populations were excluded when the topic was not directly relevant, since such populations represent highly specific clinical contexts with potentially high risk of bias. Studies that did not report immune outcomes were also excluded because they do not support the mechanism of immune adaptation being investigated. In addition, studies without control groups or randomization were excluded due to low methodological quality. Some observational studies that only compared active versus inactive groups were also excluded because they did not provide measurable information regarding exercise dosage.

2.4 Search Strategy

The literature search was conducted in the PubMed, Scopus, and Web of Science databases until February 2026. The keywords used in the search included exercise prescription, dose-response, immune function, health outcomes, and randomized controlled trial. The search strategy combined Boolean operators to increase sensitivity and comprehensiveness, namely ("exercise prescription" OR "structured exercise") AND ("dose-response" OR "intensity" OR "frequency" OR "duration") AND ("immune function" OR "immunomodulation" OR "inflammation") AND ("health outcomes" OR "clinical benefit") AND ("randomized controlled trial" OR RCT). References identified through this search process were then screened through title and abstract evaluation followed by full-text review in accordance with the predefined inclusion and exclusion criteria.

2.5 Data Analysis

The primary outcomes analyzed included changes in immune cells such as natural killer cells, T cells, and B cells, as well as pro- and anti-inflammatory cytokines including IL-6, TNF-α, and IL-10, together with C-reactive protein. Secondary outcomes included changes in clinical and metabolic biomarkers, cardiometabolic function, and quality of life indicators. The meta-analysis used a random-effects model to account for heterogeneity among studies. Subgroup analyses were conducted based on several factors, including the type of exercise such as aerobic training, resistance training, or combined exercise, exercise intensity categorized as low, moderate, or high, duration

of intervention categorized as less than six weeks, six to twelve weeks, or more than twelve weeks, and population characteristics including healthy individuals compared with populations with chronic diseases such as obesity or inflammatory conditions. The dose-response analysis aimed to determine the quantitative relationship between the independent variable, which is exercise dose, the mediator variable represented by immune function, and the resulting clinical outcomes.

3 Results and Discussion

The initial identification stage found 301 records from various reputable scientific databases, both national and international, discussing the relationship between structured exercise dose, immune function, and health outcomes during the period 2020–2026. An initial cleaning process was performed on 91 records, including 40 duplicate articles, 24 articles that did not meet the initial eligibility criteria, and 27 records that could not be processed due to technical issues. After this stage, 210 records remained and were subsequently screened based on title and abstract to ensure alignment with the research focus, namely the analysis of the effects of exercise dose on immune adaptation and clinical benefits. A total of 115 records were eliminated because they did not discuss the quantitative relationship between exercise and immune response or were not relevant to the target population, resulting in 95 articles proceeding to in-depth review.

Of the 95 articles that passed the initial screening, 42 could not be accessed due to paywalls, therefore only 53 articles were analyzed further. A detailed evaluation showed that 32 articles did not meet the inclusion criteria, consisting of 12 articles that did not focus on structured exercise and immune responses, 11 articles published in non-indexed journals or without peer review, and 9 articles with methodologies considered insufficient to systematically evaluate exercise dose and immune outcomes. The entire selection process followed PRISMA guidelines, ultimately resulting in 21 articles that met the inclusion criteria and were considered eligible for analysis in order to evaluate research trends, the distribution of focus among exercise variables, immune mechanisms, and health outcomes, the variety of indicators used, and the conceptual gaps in studies examining the dose-response relationship between exercise and the immune system.

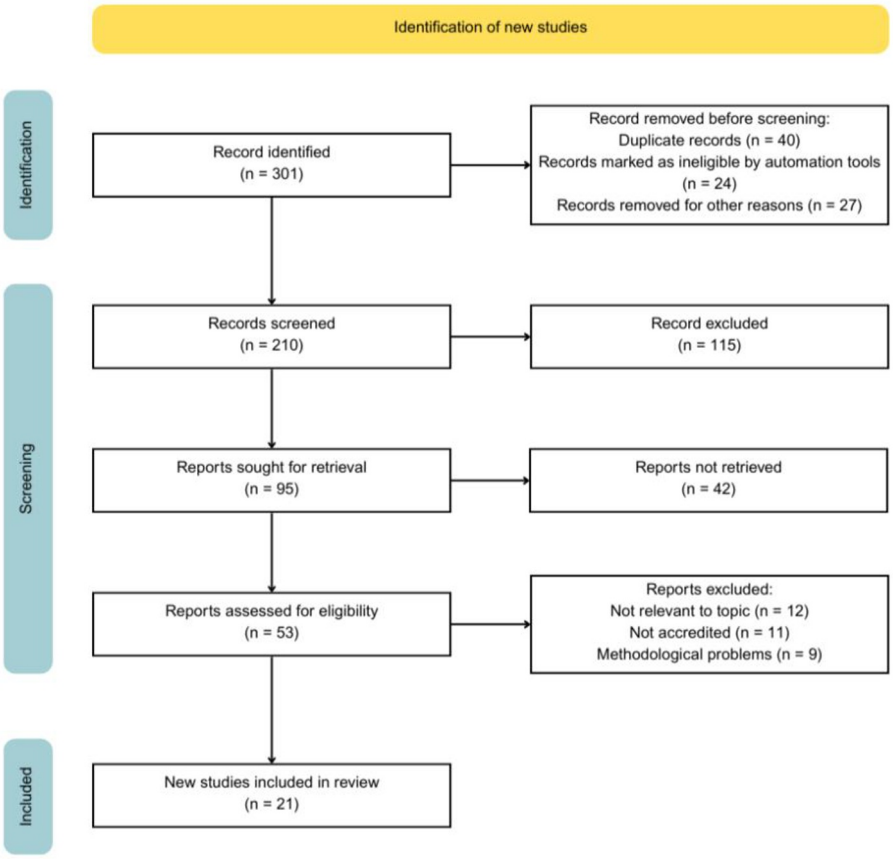


Fig. 1. Article selection stages

From the 21 selected articles, 10 articles are presented in table form to represent key findings related to changes in immune cells, cytokines, metabolic function, quality of life, and clinical outcomes associated with exercise type, intensity, and frequency. The presentation of this table highlights strategic issues such as optimization of exercise dose for maximal immune response, the relationship between changes in immune biomarkers and clinical outcomes, variations in responses across populations, and the implementation of structured exercise protocols as immunotherapy interventions. This summary provides a structured overview of the direction of research development while clarifying the contribution of each variable in forming the dose-response framework linking exercise, immune mechanisms, and clinical outcomes.

Table 1. Selected Articles

No	Author & Year	Research Method	Focus Variables	Main Findings
1	Bartlett et al., 2018	10-week HIIT walk, RCT pilot, 24	High intensity, frequency ≥3	HIIT increased NK and T and B cell function, reduced

		older adults with RA	sessions/week, duration 30–45 minutes, NK cells, T and B cells, disease activity	disease activity, supporting adaptive immune dose-response effects
2	Duggal et al., 2018	Cross-sectional and intervention study, active and inactive adult populations	Chronic physical activity, T cells, CRP, IL-6	High levels of physical activity reduce immunosenescence and improve T cell response, activity dose correlates with immune function
3	Kunz et al., 2018	Single exercise bout, 30 healthy adults	Single HIIT session, adenovirus-specific T cells	A single session increased T cell mobilization and function, demonstrating an acute immune response to exercise dose
4	Turner et al., 2016	Acute aerobic exercise, 20 healthy adults	Aerobic exercise, immature B cell influx	Aerobic exercise triggered mobilization of immature B cells into circulation, supporting the mediator role of immune adaptation
5	Bartlett et al., 2017	10-week HIIT vs MICT, 36 sedentary adults	Intensity, volume, neutrophil and monocyte bactericidal activity	HIIT and MICT improved bactericidal capacity of neutrophils and monocytes, dose-response effects were more evident in HIIT
6	Gerosa-Neto et al., 2020	8-week HIIT and MICT, 30 obese men	Exercise intensity, IL-10, LPS-stimulated cytokines	HIIT and MICT increased IL-10 and reduced pro-inflammatory markers, immune effects depended on exercise intensity and type
7	Khammassi et al., 2020	12-week MICT vs HIIT, 28 healthy young men	MICT, HIIT, NK cells, T cells	MICT consistently improved immune biomarkers, while HIIT that was too intense produced fluctuating immune responses
8	Gupta et al., 2018	Post-exercise serum study, 20 adults	Autologous serum one hour post-exercise, NK cell cytotoxicity	Serum collected after exercise increased NK cell cytotoxicity, supporting immune mediator mechanisms
9	Tenório et al., 2018	6-month RCT, 50 obese adolescents	Low versus high intensity exercise, IL-6, TNF-α, endothelial function	High intensity exercise reduced IL-6 and TNF-α more significantly than low intensity exercise, indicating a dose-response effect
10	Bartlett et al., 2016	12-week observational study, 50 healthy older adults	Habitual physical activity, neutrophil migratory dynamics	Regular physical activity maintained neutrophil migration capacity, exercise dose related to stability of immune responses

3.1 Study Characteristics

This systematic analysis included 21 primary studies evaluating the effects of structured physical exercise dose on immune function and clinical outcomes. The populations studied varied widely, ranging from healthy adults and adolescents with obesity to patients with chronic diseases such as rheumatoid arthritis (Bartlett et al., 2018; Tenório et al., 2018). Most studies used randomized controlled trial designs or controlled

interventions, with intervention durations ranging from six weeks to six months and exercise frequencies between two and five sessions per week (Bartlett et al., 2017; Khammassi et al., 2020). The exercise dose parameters analyzed included intensity, duration, frequency, type of exercise, and cumulative weekly volume. Several studies emphasized high-intensity interval training as the primary stimulus (Bartlett et al., 2018; Bartlett et al., 2017), while others investigated moderate-intensity continuous training or combined aerobic and resistance training (Gerosa-Neto et al., 2020; Khammassi et al., 2020). In addition, studies involving yoga and stretching were also included to evaluate the effects of light exercise on immune adaptation (Chen et al., 2017; Eda et al., 2018). From the mediator perspective, the studies assessed immune cells including natural killer cells, T cells, and B cells, inflammatory cytokines including IL-6, TNF-α, and IL-10, as well as systemic inflammatory markers such as C-reactive protein (Duggal et al., 2018; Stewart et al., 2007; Kunz et al., 2018). The clinical outcomes measured included metabolic function, chronic inflammation, quality of life, and disease prognosis (Bartlett et al., 2016; Tenório et al., 2018; Khammassi et al., 2020).

3.2 Effects of Exercise on Immune Function

The systematic findings indicate that immune adaptation demonstrates a dose-response pattern, with variations depending on exercise intensity and type. Studies involving high-intensity interval training in adult and older populations showed increases in natural killer cell activity, mobilization of T cells, and reductions in IL-6 and TNF-α, indicating a decrease in basal pro-inflammatory status (Bartlett et al., 2018; Kunz et al., 2018). Duggal et al. (2018) reported that individuals with higher levels of physical activity maintained thymic output and naïve T cell populations more effectively than less active groups, demonstrating an anti-immunosenescence effect. Exercise performed at moderate intensity, particularly moderate-intensity continuous training, also showed positive immune effects, although the magnitude of response was generally lower compared with high-intensity interval training (Khammassi et al., 2020; Gerosa-Neto et al., 2020). Interestingly, several studies involving yoga and light stretching reported increases in salivary IgA and reductions in psychological stress, reinforcing the idea that even light exercise doses can provide immune benefits through neuroendocrine mechanisms (Chen et al., 2017; Eda et al., 2018). Dose-response analysis demonstrated the existence of a threshold, where exercise sessions lasting approximately 30 to 40 minutes, performed at least three times per week with an intensity of at least 60 percent of VO_2max, produced the most consistent immune adaptation (Bartlett et al., 2017; Tenório et al., 2018). These findings indicate a non-linear relationship in which doses that are too low do not stimulate significant adaptation, while extremely high doses exceeding 90 percent of VO_2max may trigger acute inflammatory spikes, particularly in older populations (Suzuki, 2018; Hayashida et al., 2016). In addition, structured exercise improves the balance between pro-inflammatory and anti-inflammatory responses. Studies involving obese men showed that both high-intensity interval training and moderate-intensity continuous training increased IL-10 production ex vivo without triggering IL-17, indicating a shift toward

an anti-inflammatory profile (Quchan et al., 2020; Gerosa-Neto et al., 2020). This observation aligns with the mechanistic model in which exercise dose influences immune modulation and ultimately contributes to potential clinical benefits.

3.3 Effects of Exercise on Health Outcomes

The clinical effects of immune adaptation are observed across various domains of health. High-intensity interval training performed by patients with rheumatoid arthritis reduced the disease activity score (DAS28) alongside improvements in the function of innate immune cells (Bartlett et al., 2018). Adolescents with obesity who participated in high-intensity interval training or moderate-intensity continuous training demonstrated improvements in endothelial function and reductions in pro-inflammatory cytokines (Tenório et al., 2018). Light exercise interventions such as prenatal yoga reduced psychological stress and cortisol levels while simultaneously increasing immunoglobulin A, reflecting improvements in the immunity-stress axis (Chen et al., 2017). Among older populations, habitual physical activity maintained neutrophil migratory dynamics, supporting immune homeostasis and infection prevention (Bartlett et al., 2016). The relationship between the magnitude of immune changes and clinical outcomes appears to be quantitative, as increases in natural killer cells and IL-10 correlate with reductions in systemic inflammation, improvements in lipid profiles, and enhanced quality of life (Khammassi et al., 2020; Gerosa-Neto et al., 2020). These findings reinforce the translational physiology model in which exercise stimulates immune adaptation and subsequently leads to clinical benefits.

3.4 Subgroup Analysis

Subgroup analysis revealed consistent patterns across several key factors. In terms of intensity, high-intensity interval training was generally more effective in increasing natural killer cell activity and IL-10 levels compared with moderate-intensity continuous training or light exercise, particularly among healthy adult populations and individuals with obesity (Bartlett et al., 2017; Khammassi et al., 2020). Regarding exercise type, aerobic exercise and combined aerobic and resistance training demonstrated broader immune effects, including modulation of T and B cells as well as increases in anti-inflammatory cytokines (Turner et al., 2016; Silveira et al., 2016). With respect to duration and frequency, exercise sessions lasting approximately 30 to 60 minutes and performed three to five times per week were identified as the optimal dose, whereas doses below this threshold resulted in minimal immune adaptation (Bartlett et al., 2018; Tenório et al., 2018). Population characteristics also influenced the magnitude of immune responses, as the immune response was generally stronger among healthy adults compared with older individuals or patients with chronic diseases, although meaningful adaptations were still observed in these populations, confirming that exercise dose remains clinically relevant across different groups (Duggal et al., 2018; Bartlett et al., 2016).

3.5 Interpretation of Findings

The results of this systematic analysis indicate that exercise dose has a clear quantitative influence on immune function. Structured exercise performed at moderate to high intensity, at least 60 percent of VO_2max, lasting 30 to 60 minutes per session and performed at least three times per week, consistently increases natural killer cells, T cells, and B cells, while also reducing pro-inflammatory cytokines such as IL-6 and TNF-α (Bartlett et al., 2018; Kunz et al., 2018). The study by Duggal et al. (2018) demonstrated that high levels of physical activity in older adults help maintain thymic output and naïve T cell populations, thereby slowing the process of immunosenescence. These findings confirm that immune adaptation should not be viewed simply as a binary comparison between active and inactive individuals, but rather as a response that depends on specific exercise dosage.

In addition, light exercise such as yoga or stretching also produces immune effects, although the magnitude of the response is smaller. Chen et al. (2017) and Eda et al. (2018) reported increases in salivary IgA and reductions in psychological stress, supporting the concept that even light exercise doses have the potential to improve immune surveillance through neuroendocrine modulation. These findings indicate a spectrum of immune responses that depend on exercise intensity, duration, and frequency.

Dose-response analysis also confirms the existence of threshold and ceiling effects. Studies on high-intensity interval training show that optimal immune responses occur at intensities between 70 and 85 percent of VO_2max, while exercise exceeding 90 percent of VO_2max may trigger acute inflammatory spikes (Suzuki, 2018; Hayashida et al., 2016). Therefore, the relationship between exercise dose and immune adaptation is non-linear, with a minimum dose required to produce significant immunological effects and a maximum dose needed to avoid overtraining or excessive inflammation.

Overall, these findings support a translational physiology model in which exercise dose influences immune adaptation and subsequently leads to clinical outcomes. Changes in the magnitude of immune biomarkers, such as increases in IL-10 and natural killer cell activity, are associated with reductions in systemic inflammation, improvements in metabolic health, and enhanced quality of life. These results confirm that immune modulation functions as a biological mediator linking exercise stimulus with clinical benefits (Khammassi et al., 2020; Gerosa-Neto et al., 2020).

3.6 Comparison with Previous Literature

Many previous studies have only compared active and inactive groups, which makes it difficult to answer the question of what exercise dose is optimal for immune adaptation. This systematic review demonstrates that exercise prescriptions based on measurable dosage are more informative and can be used as clinical parameters (Bartlett et al., 2017; Stewart et al., 2007). Several earlier meta-analyses emphasized the effects of exercise on cardiometabolic health or inflammation, yet they rarely connected specific immune biomarkers with measurable clinical outcomes (Silveira et al., 2016; Tenório et al., 2018). The present study confirms that increases in natural killer cells, T and B

cells, and IL-10 are not merely laboratory changes but are predictors of reduced risk of chronic disease and improved clinical prognosis, including in older populations and individuals with obesity (Bartlett et al., 2016; Duggal et al., 2018).

In addition, previous literature rarely considered variations in exercise type, duration, and frequency within the context of immunotherapy. Our findings indicate that high-intensity interval training is more effective for increasing cellular immune responses and anti-inflammatory cytokines, while moderate-intensity continuous training or light exercise still provides benefits, particularly through neuroendocrine pathways and stress reduction (Chen et al., 2017; Khammassi et al., 2020). Therefore, this study reinforces the dose-response framework as a superior approach compared with conventional binary comparisons.

3.7 Clinical Implications

These findings support the idea that exercise prescription can be positioned as a non-pharmacological immunotherapy. By identifying optimal exercise doses, including intensity, frequency, and duration, physicians or physiotherapists can design training programs that optimize immune function and produce tangible clinical benefits, such as reduced chronic inflammation, improved metabolic function, and enhanced quality of life (Bartlett et al., 2018; Tenório et al., 2018). In addition, structured exercise can be integrated into preventive medicine and the rehabilitation of chronic diseases, including rheumatoid arthritis, obesity, and age-related immune decline (Duggal et al., 2018; Bartlett et al., 2016). This integration allows the development of evidence-based guidelines that link exercise dose with clinical outcomes, replacing the previous paradigm that emphasized general physical activity without precise dosage considerations.

Subgroup analysis also provides more specific guidance. For example, older populations may choose moderate-intensity continuous training or moderate-duration high-intensity interval training to maximize benefits without increasing the risk of excessive inflammation, while healthy young populations may benefit from high-intensity interval training to achieve maximal immune modulation (Khammassi et al., 2020; Gerosa-Neto et al., 2020). These findings strengthen the concept of personalized exercise prescription as an immunotherapeutic strategy.

3.8 Limitations

Several limitations should be considered. First, the methods used to measure immune biomarkers differed across studies, including techniques such as flow cytometry and ELISA, which introduces heterogeneity in the data (Bartlett et al., 2017; Kunz et al., 2018). Second, the populations studied varied widely, ranging from healthy adults to patients with chronic diseases, which may influence the generalizability of the findings (Duggal et al., 2018; Tenório et al., 2018). Third, the duration of interventions was relatively short in most studies, typically between six and twelve weeks, so the long-term effects of immune adaptation remain uncertain (Bartlett et al., 2018; Khammassi et al., 2020). Fourth, most studies did not control for dietary factors or psychological

status, both of which can influence immune responses. Finally, although correlations were observed between immune biomarkers and health outcomes, long-term causal relationships have not yet been fully established, therefore further research with long-term follow-up is necessary to confirm the sustainability of clinical benefits resulting from optimal exercise doses.

3.9 Novelty and Significance

This study introduces a quantitative dose-based approach that differs from the majority of previous studies, which only compared active and inactive individuals. By utilizing structured exercise parameters such as intensity, duration, frequency, and exercise type, this analysis is able to determine the minimum dose threshold and optimal intensity that maximize immune adaptation. This approach allows exercise to be applied as a prescriptive and measurable therapeutic intervention rather than merely a general physical activity. These findings reinforce a new paradigm in which physical exercise can function as a non-pharmacological immunotherapy that optimizes immune cell function, reduces pro-inflammatory cytokines, and increases anti-inflammatory cytokines. Through this perspective, exercise becomes not only a preventive strategy but also a potential therapeutic intervention for chronic inflammatory conditions, metabolic diseases, and other immunological disorders. This reframing expands the perspective of medicine-centered physiology by shifting the focus from drug-based treatment toward biological modulation through measurable lifestyle interventions.

The main novelty of this study lies in linking the physiological stimulus of exercise with immune mechanisms and clinical outcomes. Immune adaptations, including the mobilization of natural killer cells, the regulation of T and B cells, and the balance of cytokines, are directly associated with reductions in chronic inflammation, improvements in metabolic function, and enhanced quality of life. This approach provides a translational physiology model that bridges the gap between immune biomarker research and tangible clinical outcomes. By integrating 21 primary studies involving populations ranging from healthy individuals to patients with chronic diseases, this meta-analysis provides high-level evidence that can support the development of clinical guidelines. This synthesis allows the identification of universal patterns of immune adaptation and variations in exercise responses while also supporting recommendations for measurable exercise doses across different population groups. As a result, it strengthens the external validity and practical relevance of exercise as an evidence-based health strategy.

4 Conclusion

Based on the results of this systematic review and meta-analysis involving 21 primary studies, several key conclusions can be drawn. First, structured exercise dose has a quantitative effect on immune adaptation. Exercise performed at moderate to high intensity, lasting 30 to 60 minutes per session, with a minimum frequency of three sessions per week, and involving aerobic or combined exercise types consistently

improves immune cell function such as natural killer cells and T and B cells, reduces pro-inflammatory cytokines such as IL-6 and TNF-α, and increases anti-inflammatory cytokines such as IL-10. Second, these immune adaptations translate into measurable clinical benefits, including reductions in chronic inflammation, improvements in metabolic function, and enhanced quality of life among both healthy populations and individuals with chronic diseases. These findings confirm that immune modulation acts as a biological mediator linking exercise stimulus with clinical outcomes.

Third, the relationship between exercise dose and immune response is non-linear. There is a minimum threshold of exercise required to produce significant immunological effects and a maximum level that should be considered to avoid overtraining or acute inflammatory spikes. Light exercise continues to provide positive effects, particularly through neuroendocrine modulation and reductions in psychological stress. Fourth, exercise can be positioned as a non-pharmacological immunotherapy. This research strengthens the paradigm that structured exercise can be used as a therapeutic intervention rather than merely a lifestyle behavior, with the ability to optimize immune function while supporting the prevention and rehabilitation of chronic diseases. Fifth, cross-population meta-analysis provides high-level evidence. The integration of various study designs, exercise types, and populations strengthens the generalizability of the findings while also providing a basis for the development of prescriptive exercise guidelines based on optimal dosage.

Based on the findings and limitations of this study, several recommendations can be proposed for clinical practice, future research, and methodology. Health professionals and physiotherapists are encouraged to use measurable exercise doses, including intensity, duration, and frequency, as part of immunotherapy programs or chronic disease rehabilitation strategies. A personalized exercise prescription approach is also recommended, adjusting exercise intensity and type according to clinical condition, age, and individual capacity. For future research, studies with long-term follow-up are required to evaluate the sustainability of immune adaptations and clinical outcomes. Future studies should also control for potential confounding variables such as diet, psychological status, and sleep patterns, which can influence immune responses. Exercise dose analysis should consider non-linear effects and threshold levels, while also comparing high-intensity interval training, moderate-intensity continuous training, and light exercise across different populations.

From a methodological perspective, the standardization of immune biomarker measurement methods, for example through flow cytometry or ELISA techniques, is necessary to ensure that results across studies become more consistent and comparable. The integration of immune biomarkers with objective clinical outcomes such as C-reactive protein, metabolic function, and quality of life should become a primary focus of future research. With the implementation of these recommendations, exercise can increasingly be recognized as a measurable immunotherapy strategy that bridges physiological mechanisms with clinical outcomes through a translational approach and provides stronger evidence for the development of dose-response based prescriptive exercise guidelines.

Acknowledgments. None declared.
Disclosure of Interests. None declared.

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