A Scoping Review on the Effects of Physical Exercise and Fitness on Peripheral Leukocyte Energy Metabolism in Humans

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ABSTRACT

Background: Both acute and chronic exercise have profound effects on systemic metabolism and the immune system. While acute exercise transiently disturbs energy homeostasis and elicits acute inflammation, exercise training improves systemic metabolic capacity, lowers basal inflammation, and reduces infection risk. Accordingly, accumulating evidence indicates links between systemic and immune cell metabolism and suggests that cellular metabolism may be an important way exercise influences immune function. Yet, no reviews have systematically surveyed the literature in this area. Aims: The aims of this scoping review were to collect, summarize, and provide descriptive analysis of literature on the effects of acute exercise, chronic exercise, and physical fitness on peripheral leukocyte energy metabolism of human adults. Methods: Reports were retrieved from the databases Pubmed, Scopus, and Embase and hierarchically filtered for eligibility. Eligible reports were those that implemented acute or chronic exercise interventions, or assessed physical fitness, in relation to the regulation or function of leukocyte energy metabolism in human adults. Data were charted from eligible reports by two independent reviewers, confirmed by conference, and organized for reporting. Results & Conclusion: Results suggest acute exercise can influence the regulation and function of leukocyte metabolism, with some similarities to what has been previously documented in skeletal muscle. Data also evidence that exercise training and/or physical fitness alters cellular metabolic regulation and function. Improvements in markers of cell respiratory function or mitochondrial regulation were frequently observed following training or with greater fitness. However, notable gaps in the literature remain. These gaps include: the effects of acute exercise and exercise training on leukocyte glycolysis, the effects of resistance and concurrent exercise, and potential differences in the effects of exercise between immune cell types and subsets. Future research is encouraged to fill the latter gaps and further delineate how exercise influences the immune system and can be used to support overall health.

Keywords: Exercise, Physical Fitness, Human, Leukocyte, Metabolism

INTRODUCTION

Physical exercise is essential to maintaining or improving physical and physiological function and preventing disease. Exercise training is a preventative measure against the development of multiple chronic diseases (8), and higher levels of both cardiorespiratory fitness and physical strength are negatively correlated with all-cause mortality (37, 39). These beneficial effects appear to arise from compensatory responses elicited by the stress of each exercise bout, that summate to enhanced function (30). While acute exercise results in metabolic perturbation proportional to its intensity and duration, training leads to improved efficiency of and capacity for energy production that lessens the stress of a given workload. This has been well demonstrated both systemically and at the level of skeletal muscle (30, 32). Similarly, acute exercise provokes an inflammatory immune response that scales with workload (i.e., greater inflammation following prolonged and intense exercise), while exercise training diminishes basal inflammation and risk for infection (71).

The parallel effects of exercise on energy metabolism and the immune system are particularly intriguing given the profound role of cellular metabolism in determining immune cell phenotype and function (52). Broadly, quiescent, regulatory, and memory cells are fueled by mitochondrial oxidation of fatty acids and carbohydrates, while activated and effector cells are biased towards the use of glycolysis (52). Stimulation of macrophages (e.g., with lipopolysaccharide) and T cells (e.g., with anti-CD3 and anti-CD28 antibodies) shifts metabolic poise from mitochondrial respiration to glycolysis, ostensibly to fuel inflammatory processes and/or proliferation (45, 52, 60). In contrast, mitochondrial fatty acid oxidation is characteristic of anti-inflammatory (i.e., M2-like) macrophages and regulatory T cells, and appears to constrain inflammation when enforced (45, 68). However, mitochondrial respiration is not the strict domain of quiescent and regulatory cells. Mitochondrial respiration also appears necessary for initial T cell activation, memory transition, and persistent function (9, 25, 62, 72). Likewise, inflammatory (i.e., M1-like) macrophages utilize mitochondrial flux to generate inflammatory cytokines and reactive oxygen species (ROS) (46). Together, data collected to date emphasize fundamental links between cellular metabolic programs and immune cell form and function.

A variety of methods exist for investigating cellular metabolism, including within cells of the immune system. Though complete survey of these methods is beyond the scope of this review, a brief summary will be provided to aid interpretation of the current results. Those interested in additional detail may find references (5), (35), (54), (55), and (70) useful. In general,

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measures of cellular metabolism may be categorized as either assessing metabolic regulation or metabolic function. Metabolic regulation includes assessments of gene and protein-level expression for components of fuel oxidation and ATP generation, as well as assessments of the state of cell mitochondria. Examples include gene or protein-level expression of targets regulating glycolysis (e.g., hexokinase), cellular respiration (e.g., cytochrome c oxidase), and mitochondrial homeostasis (e.g., mitofusin). Assessments of mitochondrial mass and membrane polarity contribute information on cells' metabolic state and capacity for mitochondrial respiration. Measures of metabolic function include assays of enzyme activity (e.g., lactate dehydrogenase), fuel oxidation and generation of intermediates (e.g., fatty acid oxidation), as well as real-time assessments of metabolic pathway function (e.g., cellular respiration). Common platforms for probing cellular metabolic function include Agilent Seahorse Analyzers and Oroboros' O2k-Respirometer. Both estimate cellular metabolic function, over time and in response to various metabolic inhibitors, through measurement of oxygen consumption and/or proton efflux to provide evidence of mitochondrial respiration and glycolytic flux.

The acute and chronic effects of exercise on systemic and cellular metabolism suggest that cellular metabolic changes may be an important means by which exercise alters immune function. For instance, the coincident mobilization of energy substrates (e.g., glucose from liver, fatty acids from adipose tissue) and leukocytes during acute exercise may both bias the mobilized leukocytes towards inflammatory action and support effector cell function fueled by glycolysis (28, 52, 61). In contrast, oxidative adaptations similar to those observed in skeletal muscle could support memory cell formation following pathogen encounter, as well as promote anti-inflammatory cell function (43, 46, 72). Recent publications support the hypothesis that differences in immune function associated with exercise and physical fitness are related to cellular metabolic changes (6, 41). Yet, to our knowledge no reviews have yet surveyed the literature regarding the metabolic effects of exercise within the immune system. Consequently, the aim of this scoping review is to collate, summarize, and provide a descriptive analysis of research on the effects of acute exercise and chronic exercise on leukocyte energy metabolism. Relatedly, we also sought to summarize research on the relationships between physical fitness and leukocyte energy metabolism.

METHODS

Overview

This review adopted the scoping review framework proposed by Arksey and O'Malley (4). Namely, we: 1) identified the research question, 2) identified relevant literature, 3) reviewed and selected studies, 4) charted the data, 5) collated and summarized the results for reporting. The review was guided by the research question, "What is known about the effects of acute exercise, chronic exercise, and physical fitness on peripheral blood leukocyte metabolism in human adults?" For the purpose of the review, the effects of acute exercise were defined as those observed within 24 hours of an exercise bout, while the effects of chronic exercise were those observed at rest following >10 days of exercise training. Measures of physical fitness included the application of any standardized test of participant strength and/or cardiorespiratory fitness. Leukocyte energy metabolism included regulatory and/or functional assessments of cellular glycolysis and mitochondrial respiration within peripheral leukocytes. Given the relationship between leukocyte metabolism and function, measures of leukocyte function were also included. Measures of cell function included the assessment of cell activation, motility, proliferation, and cytokine or ROS production.

Literature Search Strategy

To confirm the necessity of the project, the databases Pubmed, Cochrane Library, and JBI Evidence Synthesis were searched to identify overlapping reviews (56). This search returned 0 reviews through JBI Evidence Synthesis, 0 reviews through Cochrane Library, and 56 results in Pubmed. Nineteen of the latter results were deemed potentially relevant to our research question. However, following manual review, none of the nineteen results possessed overlapping objectives to our own and this was taken

Table 1: Search Strategy Employed in Each Database

Database	Search Terms
PubMed	("cardiorespiratory fitness"[MESH] OR "cardiorespiratory fitness"[tiab] OR "Physical Fitness"[Mesh] OR "physical fitness"[tiab] OR "Physical Endurance"[Mesh] OR "physical endurance"[tiab] OR "High-Intensity Interval Training"[Mesh] OR "High-Intensity Interval Training"[tiab] OR HIIT[tiab] OR "Exercise"[Mesh] OR exercise[tiab] OR "acute exercise"[tiab]) AND ("Leukocytes"[Mesh] OR Leukocytes[tiab] OR "Leukocytes, Mononuclear"[Mesh] OR "Mononuclear Leukocytes"[tiab] OR "peripheral blood mononuclear cells"[tiab] OR "Lymphocytes"[Mesh] OR lymphocytes[tiab] OR PBMC*[tiab]) AND ("Oxygen Consumption"[Mesh] OR "Oxygen Consumption"[tiab] OR "Cell Respiration"[Mesh] OR "Cellular Respiration"[tiab] OR "Energy Metabolism"[Mesh] OR "Energy Metabolism"[tiab] OR "Oxidative Phosphorylation"[Mesh] OR "Oxidative Phosphorylation"[tiab] OR "Glycolysis"[Mesh] OR Glycolysis[tiab] OR "Mitochondrial Dynamics"[Mesh] OR "Mitochondrial metabolism"[tiab] or bioenergetic*[tiab])
Scopus	(TITLE-ABS-KEY (*"cardiorespiratory fitness"* OR *"physical fitness"* OR *"physical endurance"* OR *"High-Intensity Interval Training"* OR *exercise* OR *"acute exercise"*) AND TITLE-ABS-KEY (*leukocyte** OR *"peripheral blood mononuclear cells"* OR *lymphocyte** OR *pbmc**) AND TITLE-ABS-KEY (*"Oxygen Consumption"* OR *"Cell Respiration"* OR *"Cellular Respiration"* OR *"Energy Metabolism"* OR *"Oxidative Phosphorylation"* OR *glycolysis* OR *"mitochondrial dynamics"* OR *bioenergetic**))
Embase	(exp cardiorespiratory fitness/ or exp fitness/ or exp endurance/ or exp high intensity interval training/ or exp exercise/) and (exp leukocyte/ or exp mononuclear cell/ or exp peripheral blood mononuclear cell/ or exp lymphocyte/) and (exp oxygen consumption/ or exp cell respiration/ or exp energy metabolism/ or exp oxidative phosphorylation/ or exp glycolysis/ or exp mitochondrial dynamics/ or exp mitochondrial respiration/)

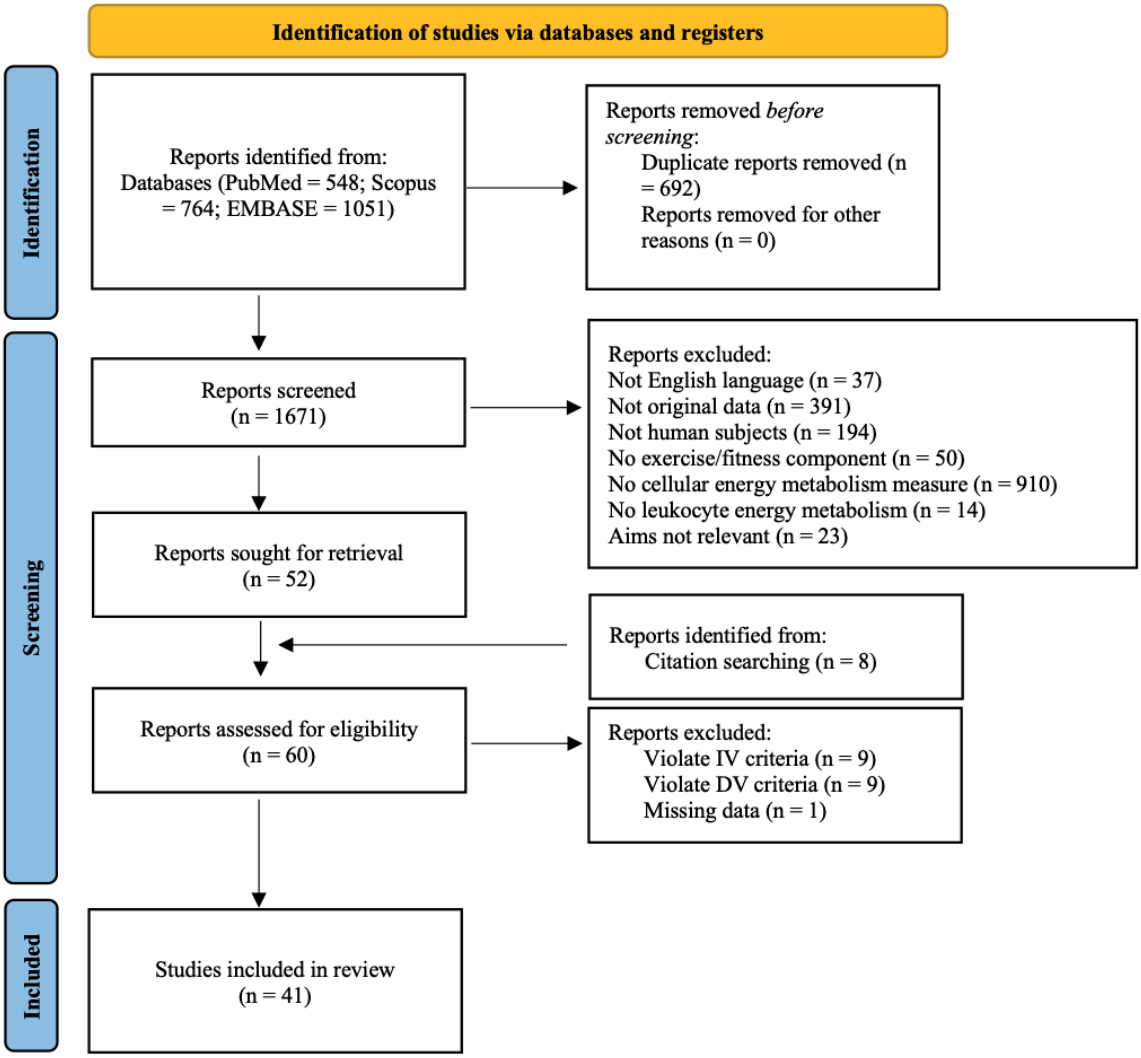

Figure 1:
Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

as justification for the current review (Supplementary Table 1).

Relevant literature was sought through the online databases PubMed, Scopus, and Embase, and review of references within selected reports. The search strategy for each database was developed between the first and last author and refined through consultation with the department librarian. The searches were designed to retrieve reports on the effects of exercise or fitness on the regulation and function of energy metabolism of peripheral leukocytes in human adults. Reports published prior to May 9, 2022 (the date of search) were considered. The search strategy for each database is listed in Table 1.

Reference Selection

Following database search, all results were compiled within a digital reference manager (Mendeley) and hierarchically filtered for relevance by two independent reviewers (CFH and MTE). Reports were evaluated for inclusion through review of bibliographic data, abstracts, and full-text as necessary. Reports were excluded if they: were duplicates, were not published in English, did not report original data (e.g., review, opinion), did not include human participants, did not quantify or classify exercise/fitness/physical activity, or did not include measures of leukocyte metabolic regulation or function. Additionally, reports were screened according to their objectives and whether outcome measures were used to assess metabolic function as opposed to other aims (e.g., mitochondrial membrane depolarization as indication of cell viability versus respiratory function). Reports deemed potentially relevant were independently reviewed in full by two reviewers (CFH and RMH), followed by conference to confirm relevance. Full-texts of potentially relevant reports identified through citation searching were also retrieved for review. Reports no longer deemed relevant following review and conference were excluded (Supplementary Table 2). No conflicts in estimation of study relevance arose between reviewers.

Data Charting

An original data charting tool was developed based on data expected to be reported, and desired for inclusion in the review. A draft of this tool was piloted against three recent reports that investigated effects of acute exercise, effects of acute and chronic exercise, or effects of physical fitness on leukocyte metabolism by the reviewers listed above. Charted data were compared between reviewers following the pilot, and the tool was then

revised to economize and standardize the charting process. A blank version of the final charting tool is available upon request. Following completion of data charting for all reports, data from each reviewer were assembled for comparison. Conflicts in the charted data were reconciled through review of the associated report. Remaining disagreement regarding interpretation of the data were resolved through discussion. The final data selected for reporting represent consensus of both reviewers.

Data Collation and Reporting

Within each report, charted data were summarized to relate key study characteristics, findings, and conclusions. Across reports, data were categorized and aggregated hierarchically according to: effect(s) investigated (acute exercise, chronic exercise, physical fitness), intensity/type of exercise or training (heavy-severe intensity aerobic, light-moderate intensity aerobic, concurrent exercise, resistance exercise), participant population(s) (athletes, healthy active, inactive and/or presence of disease), cell population (mixed cell populations, isolated cell populations), and outcomes (metabolic regulation, metabolic function, cell function).

Investigated effect(s) were categorized based on whether a single bout and/or a period of training were implemented, or cross-sectional comparisons of fitness were performed. The intensity or type of exercise was classified using the described methods into heavy-severe intensity aerobic, light-moderate intensity aerobic, concurrent exercise, or resistance exercise categories. Heavy-severe intensity aerobic exercise includes those reports which implemented acute aerobic exercise or a training program, the majority of which was in or above the heavy intensity domain. The heavy intensity domain was defined as greater than the first ventilatory threshold (i.e., >75-80% maximum heart rate, >60-65% VO_{2max}) (42, 57, 58, 63). Light-moderate intensity aerobic exercise includes those reports which implemented acute exercise or a training program, the majority of which was within or below the upper limit of the moderate intensity domain (i.e., below the lower limit of heavy intensity) (11, 57). Thus, reports classified as implementing light-moderate intensity aerobic exercise were those that occurred below the thresholds listed for heavy-severe intensity (e.g., <75-80% maximum heart rate). Concurrent exercise includes reports that implemented exercise or a training program with both resistance exercise and aerobic exercise as major components. Resistance exercise includes reports that utilized an acute session or training program of resistance exercise without any significant aerobic exercise component.

The participant population(s) was/were categorized using descriptions within report methods and results sections. "Athlete Participants" includes those reports which specifically mention recruiting professional or recreational athletes as participants, as well as those that included participants pre-screened for high cardiorespiratory fitness. "Healthy Active Participants" includes those reports which mention recruiting healthy active participants. "Inactive Participants and/or Those with Disease" includes those reports which specifically mention recruiting inactive/sedentary participants and/or participants diagnosed with a pathological condition (including obesity).

The cell population studied within a report was determined following review of report methods. "Mixed Cell Populations" includes those reports which specify obtaining data from samples with mixed populations of cells including white blood cells/leukocytes, peripheral blood mononuclear cells (PBMCs), and lymphocytes. "Isolated Cell Populations" includes those reports which specify obtaining data in specific cell types either via physical isolation (e.g., positive or negative selection) or by cell type-specific gating using flow cytometry.

Outcome measures were also determined from report methods and results sections and categorized as listed in section II-1. Additionally, given the terminology associated with real-time assessments of metabolic function, a summary of this terminology is provided to aid comprehension.

Cell metabolic function assessments provided by the Seahorse Analyzer platform include estimates of glycolytic flux (derived from either extracellular acidification rate (ECAR) or proton efflux rate (PER)) and evidence of mitochondrial respiration via oxygen consumption rate (OCR). Introduction of stimulants (e.g., glucose) and inhibitors (e.g., 2-deoxyglucose, oligomycin) is used to test the function of each pathway, and deliver parameters including basal PER/OCR, maximal PER/OCR, reserve PER/spare respiratory capacity, as well as background PER/OCR (e.g., non-mitochondrial OCR). Additional information on the Seahorse platform can be found in (70) and (5).

Metabolic function assessments provided by the Oroboros-O2K platform yield similar information as the Seahorse platform. However, differences in the approach mean that outcome measures are not equivalent. In intact cells, ATP-linked (i.e., OCR associated with production of ATP), uncoupled, maximal & reserve, and non-mitochondrial OCR can be determined following the sequential addition of respiratory chain inhibitors and uncouplers (e.g., Carbonyl cyanide-p-trifluoromethox yphenylhydrazone). Additional information about electron transport system function can be acquired by monitoring OCR of permeabilized cells in the absence and presence of substrates. This approach provides outputs including routine (without and with complex I substrates), leak (without and with complex 2 substrates), complex I-linked, complex II-linked, maximal oxidative phosphorylation (OXPHOS), and maximal electron transport system capacity (ETS) OCR. Further information on the O2k platform and its use can be found in (55) and (19).With the aforementioned caveat that methodological differences mean outputs from the two platforms are not the equivalent, the following outputs from Seahorse and O2k, respectively, provide similar information: basal OCR and routine OCR, proton leak OCR and leak OCR (both), ATP-linked OCR (both), Maximal OCR and ETS, Reserve OCR (both), non-mitochondrial OCR (both). The platform used to measure cellular respiration is indicated throughout the results.

When available, statistics regarding the magnitude of observed effects (effect size, percent change, fold change) are reported following the associated results. However, these data are not included universally as they were infrequently reported throughout the included reports.

RESULTS

Search Results

The database search returned 2363 reports: 548 from Pubmed, 764 from Scopus, and 1051 from Embase. After filtering these results, 52 reports remained. These reports, along with eight additional reports identified via references included in the latter 52, were reviewed in full to confirm their eligibility.

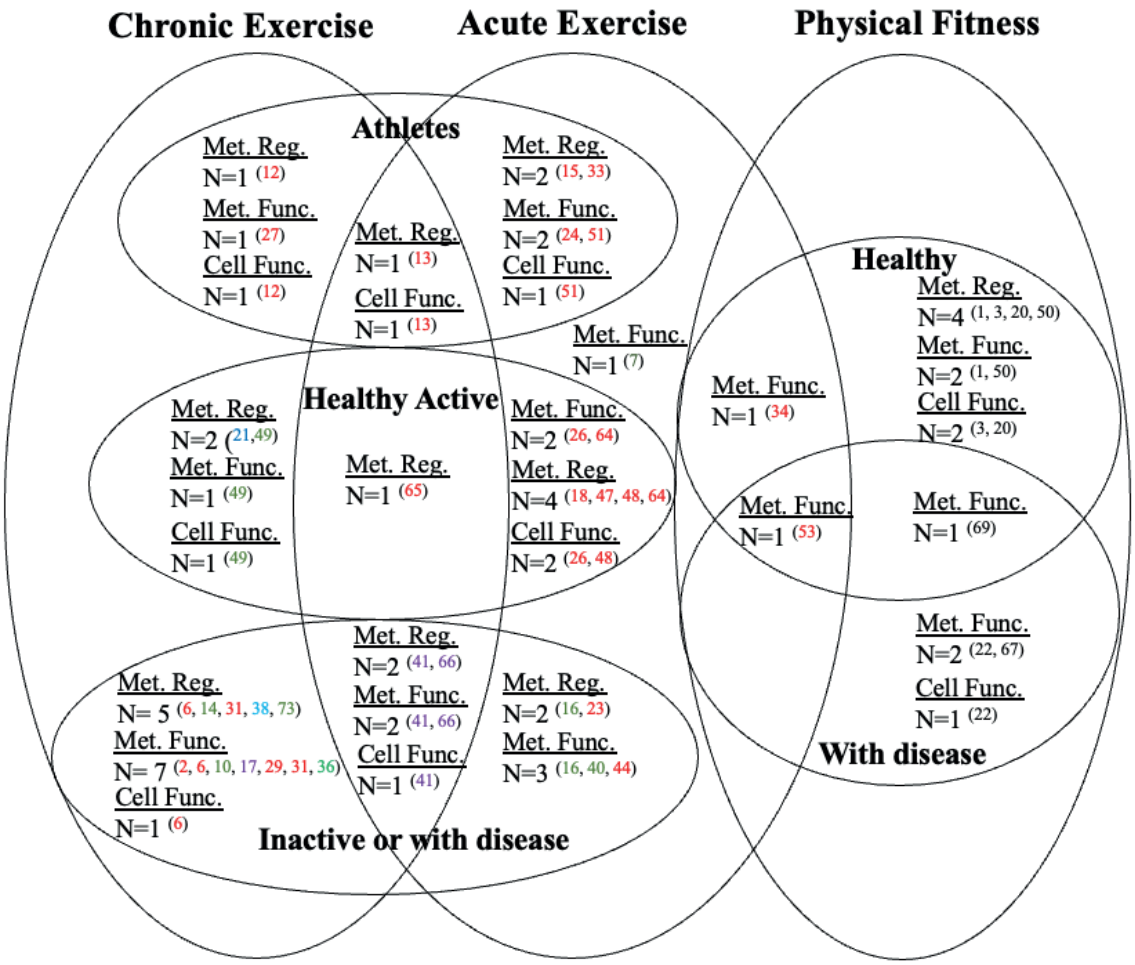

Figure 2:
Summary of experimental designs of retrieved studies examining the impacts of acute exercise, exercise training, and/or physical fitness on human leukocyte metabolic regulation (met. reg.), metabolic function (met. func.), and cell function (cell func.). Large ovals indicate whether effects of chronic or acute exercise or physical fitness were examined; areas of overlap indicate studies with a combined design (e.g., acute and chronic exercise). Smaller ovals indicate population examined; areas of overlap indicate multiple populations examined and studies appearing outside smaller ovals did not specify subject population. Number of articles investigating each of the outcome groups (met. reg., met. func., cell func.) are indicated, along with reference number. The color of the reference number indicates exercise stimulus: red: heavy-severe aerobic exercise; green: light-moderate aerobic exercise; purple: both heavy-severe and light-moderate aerobic exercise; blue: resistance or concurrent exercise.

Nineteen of the 60 reports were excluded following full-text review, leaving 41 reports for inclusion. Figure 1 relates the search and study selection process in detail.

Study Characteristics

Reports varied widely in publication date: the earliest report was published in 1958 and the latest (n=3) were published in 2022. The majority of reports were published since 2014. Most reports included study of inactive adults with or without the presence of disease (n=25), followed by those that included athletes (n=13), and then healthy active adults not formally training (n=9). In three reports the health and/or activity status of some participants could not be determined based on the methods described (3, 7, 20). Leukocyte metabolic function (e.g., cellular respiration) (n=13) was the most common study outcome, while the combination of metabolic regulation (e.g., gene expression), metabolic function, and cell function (e.g., cytolytic protein production) (n=3) was the least common.

Fourteen reports studied the effects of acute exercise on leukocyte energy metabolism (Table 2). Ten used aerobic exercise bouts of heavy-severe intensity including: three graded exercise tests to exhaustion (GXT) (15, 24, 44), four sessions of continuous cycling exercise (18, 47, 48, 64), one session of high intensity intervals (26), one session of continuous cycling ending with a time trial (33), and one pure cycling time trial (51). Four reports implemented aerobic exercise of light-moderate intensity including two bouts of treadmill walking (7, 23) and two bouts of continuous cycling (16, 40). It should be noted that the moderate exercise session in one of the latter four reports was conducted under hypoxic conditions (16).

Fourteen reports investigated the effects of chronic exercise training (i.e., >10-day exercise program) (Table 3). Seven of these reports implemented aerobic exercise of heavy-severe intensity including four programs of high-intensity interval training (HIIT) (2, 6, 17, 31), one program of sprint interval training in hypoxia (27), one program of treadmill exercise (29), and one program of sport-specific training (12). Six reports evaluated the effects of aerobic exercise training of light-moderate intensity. These included two programs of treadmill walking (14, 73), two programs of mixed aerobic exercise (10, 36), one program of continuous cycling (17),

and one trekking program (49). Additionally, one report used concurrent training (38) and one report implemented resistance training (21).

Seven reports evaluated the effects of physical fitness on leukocyte energy metabolism (1, 3, 20, 22, 50, 67, 69). Characteristics of these reports are related in Table 4.

Six reports examined the combination of acute exercise and physical fitness or exercise training on leukocyte energy metabolism (Table 5). Two reports evaluated the effects of acute heavy-severe intensity aerobic exercise amongst individuals of different levels of physical fitness (34, 53), while four reports evaluated effects of both acute and chronic exercise (i.e., acute exercise before and/or after training). Three of these studied the effects of acute aerobic exercise of heavy-severe intensity including one GXT (41), one continuous cycling bout (65), and one session of sport-specific training (13). One report studied the effects of acute cycling exercise of light-moderate intensity under hypoxic conditions (66). Regarding exercise training, three of the reports included at least one study arm of aerobic exercise training of heavy-severe intensity including: two HIIT programs (41, 66), one program of continuous and HIIT cycling (65), and one program of sport-specific training (13). Finally, two of the reports included aerobic exercise training of light-moderate intensity (41, 66). Both reports used programs of continuous cycling.

Key Findings

Effects of Acute Exercise

Key findings obtained from reports on the effects of acute exercise are related in the following sections and in Table 6. These include findings from reports strictly investigating acute exercise, and acute exercise results from those investigating both chronic and acute exercise or physical fitness and acute exercise. For reports on both acute and chronic exercise, results related in this section are restricted to those obtained prior to training or at a single timepoint following training (i.e., no pre-training acute exercise). Unless otherwise noted, data relate to pre-exercise vs. immediately post-exercise changes.

HEAVY-SEVERE INTENSITY AEROBIC EXERCISE: ATHLETE PARTICIPANTS

Mixed Cell Populations

Metabolic Regulation: Three reports investigated the effects of acute aerobic exercise of heavy-severe intensity on metabolic regulation of PBMCs among athletes. Busquets-Cortes et al. evaluated the effects of an acute bout of fitness testing and sport training following eight weeks of training and competition among professional athletes (football/soccer players) (13). No acute exercise testing was performed prior to training. In PBMCs obtained two hours following the acute bout, the authors observed increases in cytochrome C oxidase subunit IV (COXIV), peroxisome proliferator-activated receptor α coactivator 1-alpha (PGC-1α), and mitochondrial NADH dehydrogenase subunit 5 mRNA, as well as PGC-1α, mitochondrial uncoupling protein 2, and mitofusin-2 protein levels (13). Similarly, in trained cyclists, Hunter et al. observed decreased PGC-1α DNA methylation and increased PGC-1α mRNA expression in PBMCs obtained immediately following a bout of cycling exercise (33). In contrast, Capo et al. observed no change in PGC-1α, peroxisome proliferator-activated receptor γ (PPARγ), mitochondrial transcription factor A (Tfam), or mitochondrial uncoupling protein 3 mRNA, but a significant increase in mitochondrial NAD-dependent protein deacetylase sirtuin 3 (SIRT3) mRNA in PBMCs obtained two hours following GXT to exhaustion among taekwondo athletes (15).

Metabolic Function: The effects of acute aerobic exercise of heavy-severe intensity on metabolic function of mixed cell populations were investigated in three reports among athletes. In PBMCs obtained from endurance athletes immediately following GXT, Ferry et al. observed (mean ± standard deviation (SD)) 33.6 ± 6.6% decreased pyruvate dehydrogenase activity, 43.1 ± 4.7% increased citrate synthase activity, and no change in cytochrome C oxidase or succinate cytochrome reductase activities versus pre-exercise (24). Pendergast et al. also observed no change in total fatty acid (FA) oxidation in leukocytes obtained following GXT in elite runners (53). In this study, FA oxidation was determined in whole blood via oxidation of radiolabeled palmitic acid. However, FA oxidation per cell was decreased, ostensibly due to increased cell numbers. Finally, no changes in PBMC respiratory or glycolytic function (assessed via extracellular flux analyses, Seahorse Assay) were observed following one hour of cycling among trained female participants (34). However, it should be noted that blood samples were taken 21 hours post-exercise in that latter report.

Cell Function: One report assessed cell function of mixed cell populations following acute aerobic exercise of heavy-severe intensity among athletes. Intracellular ROS, and phorbol 12-myristate 13-acetate (PMA; 10ng/mL, one hour)-stimulated H_2O_2 production increased versus pre-exercise in PBMCs obtained two hours following exercise in the previously mentioned report of professional soccer players (13). In addition, increased nuclear factor kappa B (NF-κB) activation was also observed in this report. These changes in cell function occurred alongside increased gene and protein expression for markers of mitochondrial respiration and mitochondrial dynamics.

Isolated Cell Populations

Metabolic Regulation: No reports investigated the effects of acute aerobic exercise of heavy-severe intensity on metabolic regulation in isolated cell populations among athletes.

Metabolic Function: One report was retrieved on the effects of acute aerobic exercise of heavy-severe intensity on metabolic function of isolated cell populations among athletes. These authors investigated the effects of an acute 75 km cycling time trial on circulating immunomodulating factors via incubation (six hours) of THP-1 cells with athlete plasma obtained pre-exercise and various timepoints post-exercise (51). In extracellular flux experiments (Seahorse Assay), the authors observed lower OCR (measure of mitochondrial respiration) and greater ECAR (measure of glycolysis) of lipopolysaccharide (LPS)-stimulated (10 ng/mL) THP-1 cells incubated with plasma of athletes consuming only water versus those provide food during exercise (51). Spare respiratory capacity (SRC) of cells incubated with water-only plasma was also lower than the other conditions.

Cell Function: In the aforementioned study no change in

cyclooxygenase-2 mRNA expression was observed versus pre-exercise in THP-1 cells incubated (6 hours) with plasma from immediately, 1.5 hours, or 21 hours post-exercise in the water-only condition (51). Among cells incubated with 21 hours post-exercise plasma, greater cyclooxygenase-2 mRNA expression was observed in cells incubated with plasma from the water-only condition versus food conditions.

HEAVY-SEVERE INTENSITY AEROBIC EXERCISE: HEALTHY ACTIVE PARTICIPANTS

Mixed Cell Populations

Metabolic Regulation: Three reports investigated the effects of acute aerobic exercise of heavy-severe intensity on metabolic regulation of mixed cell populations among healthy active participants. Davies et al. observed elevated PGC-1α, PPARγ, and ATP-binding cassette subfamily A, member 1 (ABCA1) mRNA expression in PBMCs obtained three hours following 45 minutes cycling at 70% VO_{2max} (18). However, at the protein level, there was no significant change observed in phosphorylated AMP-activated protein kinase (AMPK). Elevated fatty acid translocase (CD36) and ABCA1 mRNA expression were also observed in PBMCs obtained at the three hour timepoint following the same prescribed exercise in a separate report (65). In contrast, Moir et al. reported decreased PGC-1α mRNA and AMPK phosphorylation in PBMCs obtained immediately following 45 minutes of cycling exercise at 70% VO_{2max} (48). Both PGC-1α mRNA and AMPK phosphorylation returned to pre-exercise levels by 1-hour post-exercise.

Metabolic Function: Two reports studied metabolic function of mixed cell populations following acute aerobic exercise of heavy-severe intensity among healthy active participants. Frisina et al. documented 18.69% increased glutamine oxidation (measured via liquid scintillation) and 27.02% increased lactate production (measured spectrophotometrically) of lymphocytes obtained three minutes following a bout of 25 one-minute high-intensity treadmill intervals (26). Furthermore, glutamine oxidation was positively correlated with percent change in NK cells ($CD56^+$) pre- to post-exercise ($r = 0.78$, $p < 0.01$), while glutamine oxidation and lactate production were negatively correlated with percent change in T cells (CD3+) pre- to post-exercise ($r = -0.93$, $p < 0.001$, $r = -0.66$, $p < 0.01$). Theall et al. observed no significant change pre- versus immediately post-exercise (30 min. at 65-75% VO_{2peak}) in PBMC routine or leak respiration, OXPHOS, or ETS per million cells as assessed by high resolution respirometry (Oxygraph) (64). However, pre- to post-exercise increases in routine ($d = 0.58$) and leak (in presence of pyruvate + malate + glutamate + succinate only) ($d = 0.80$) respiration, OXPHOS ($d = 0.80$), and ETS ($d = 0.78$) were observed when quantified per milliliter of blood.

Cell Function: Two reports studied the effects of acute aerobic exercise of heavy-severe intensity on cell function of mixed cell populations among healthy active participants. Decreased (58%) lymphocyte proliferative responses to concanavalin A (Con-A) (3.5 μg/mL, 48 hrs.) were observed following interval exercise in the report by Frisina et al. Additionally, pre- to post-exercise changes in lymphocyte proliferation positively correlated with percent change in T cells ($CD3^+$) ($r = 0.78$, $p < 0.01$) and negatively correlated with percent change in NK cells ($CD56^+$) ($r = -0.76$, $p < 0.05$) (26). The authors also report correlations between exercise induced changes in lymphocyte proliferative responses and glutamine oxidation, and lactate production. However, the directions of these relationships were not disclosed. Finally, in a separate report, decreased basal and PMA-stimulated (25 ng/mL, 10 minutes) ROS production was observed in PBMCs obtained immediately following 45 minutes cycling at 70% VO_{2max} (48). For context, decreased PGC-1α mRNA expression and AMPK phosphorylation were also observed at this timepoint in the same report.

Isolated Cell Populations

Metabolic Regulation: Two reports assessed the effects of acute aerobic exercise of heavy-severe intensity on metabolic regulation of isolated cell populations among healthy active participants. Monocytes (isolated from PBMCs via immunomagnetic separation) obtained from healthy active male participants immediately post-45 minutes of cycling exercise at 70% VO_{2max} demonstrated no change in CD36 mRNA expression but decreased AMPK phosphorylation versus pre-exercise (47). However, monocyte AMPK phosphorylation returned to baseline and CD36 remained stable one-hour post-exercise in the same report. Cycling exercise (30 minutes 65-75% VO_{2max}) was also demonstrated to alter nutrient transport and metabolism proteins of peripheral T cells. Compared to pre-exercise, increased numbers of glucose transporter type 4 positive ($GLUT4^+$) cells (+53%), but decreased proportions of hexokinase 2 positive ($HK2^+$) and numbers (-55%) and proportions of hexokinase 1 positive ($HK1^+$) CD4+ T cells were observed within post-exercise PBMCs in the report from Theall et al. (64). The authors also observed decreases in the proportions of CD36+ and HK1+ CD8+ T cells within PBMCs pre- to post-exercise. Finally, exercise-associated changes in nutrient transport and metabolism proteins were correlated with expression of a number of cell activation markers (Table 6).

Metabolic Function, Cell Function: No reports investigated the effects of acute aerobic exercise of heavy-severe intensity on metabolic function or cell function in isolated cell populations among healthy active participants.

HEAVY-SEVERE INTENSITY AEROBIC EXERCISE: INACTIVE PARTICIPANTS AND/OR THOSE WITH DISEASE

Mixed Cell Populations

Metabolic Regulation: No reports investigated the effects of acute aerobic exercise of heavy-severe intensity on metabolic regulation in mixed cell populations among inactive participants and/or those with disease.

Metabolic Function: The effects of acute aerobic exercise of heavy-severe intensity on metabolic function of mixed cell populations among inactive participants and/or those with disease were investigated in three reports. No change in PBMC respiratory or glycolytic function was observed following a one hour bout of cycling at 70% VO_{2peak} among inactive female participants in the report from Janssen et al. (34). It should be noted that post-exercise blood samples were obtained 21 hours following the original bout. Meksawan et al. and Pendergast et

al. evaluated the effects of acute treadmill GXT on leukocyte FA oxidation (whole blood oxidation of radiolabeled palmitic acid) among sedentary participants, or those with underlying pathology (44, 53). Meksawan et al. observed an increase in leukocyte FA oxidation per milliliter of blood, but a decrease when quantified on a per cell basis. Pendergast et al. also observed an increase in total leukocyte FA oxidation but no change in FA oxidation per cell among their inactive participants.

Cell Function: No reports investigated the effects of acute aerobic exercise of heavy-severe intensity on cell function, in relation to cellular metabolism, in mixed cell populations among inactive participants and/or those with disease.

Isolated Cell Populations
Metabolic Regulation: Lin et al. authored the sole report to evaluate the effects of acute heavy-severe exercise on metabolic regulation of isolated cell populations. NK cells were isolated from PBMCs via negative-immunomagnetic selection among inactive participants and/or those with disease. They observed no change in NK cell mitochondrial content or mitochondrial membrane potential (MMP), but an increase in mitochondrial oxidant burden pre- vs. post-exercise (cycle ergometer GXT) among sedentary male participants (41).

Metabolic Function: Lin et al. were also the only report to assess the effects of acute heavy-severe exercise on metabolic function of isolated cell populations among inactive participants and/or those with disease. Measurements of mitochondrial respiration were made via Oxygraph. Increases in ETS, Reserve OCR, and the bioenergetic health index (BHI) were observed in NK cells obtained immediately post-exercise versus pre-exercise (41).

Cell Function: Elevated NK cell perforin and granzyme b expression were observed immediately post- versus pre-exercise in the report from Lin et al. (41). NK cells were unstimulated in this study.

LIGHT-MODERATE INTENSITY AEROBIC EXERCISE: ATHLETE PARTICIPANTS
No reports investigated the effects of acute aerobic exercise of light-moderate intensity on cellular metabolism and function in peripheral leukocytes among athletes.

LIGHT-MODERATE INTENSITY AEROBIC EXERCISE: HEALTHY ACTIVE PARTICIPANTS
No reports investigated the effects of acute aerobic exercise of light-moderate intensity on cellular metabolism and function in peripheral leukocytes among healthy active participants.

LIGHT-MODERATE INTENSITY AEROBIC EXERCISE: INACTIVE PARTICIPANTS AND/OR THOSE WITH DISEASE

Mixed Cell Populations
Metabolic Regulation: The effects of acute aerobic exercise of light-moderate intensity on metabolic regulation of mixed cell populations were assessed in three reports. As a part of a larger investigation, Ferrer et al. instituted a 30-minute bout of treadmill walking (60-70% maximum heart rate) in older men with obesity and metabolic syndrome (23). They observed decreased COXIV and Tfam mRNA expression, and no significant change in mitochondrial respiration or mitochondrial dynamics protein levels in PBMCs obtained 30 minutes post-exercise. Similarly, Tsai et al. observed no significant changes in mitochondrial biogenesis and mitochondrial dynamics protein levels, or mitochondrial count of lymphocytes obtained following 36 minutes cycling exercise among young sedentary males (66). However, MMP was decreased and mitochondrial oxidant burden was increased following exercise. Though the absolute and relative workload of the latter bout was low (100 W, ~50% maximum Watts), it must be noted that the exercise was performed under hypoxic conditions (12% O2) (66). This undoubtedly increased the difficulty of the bout and resulting physiological responses. In contrast to Tsai et al., a separate report observed increased MMP in PBMCs obtained immediately following 40 minutes cycling exercise in hypoxia (60% $VO_{2ma}x$, 12% O2) (16).

Metabolic Function: In the same report discussed immediately previous (16), no differences in routine or maximal mitochondrial OCR measured by Oxygraph were observed post-exercise versus pre-exercise. However, the authors did report depressed OCR specifically via respiratory chain complex I (CI) in permeabilized cells. Depressed CI OCR (also measured by Oxygraph) post-exercise was also observed in permeabilized lymphocytes following exercise in hypoxia in the report from Tsai et al. (66). Additionally, these authors noted decreased OCR through complex II (CII) in permeabilized cells, decreased ATP-linked and Reserve OCR in intact cells, increased lactate dehydrogenase and glutamate dehydrogenase enzyme activity, and decreased citrate synthase activity post- versus pre-exercise (66). Depressed metabolic function following exercise is not a universal finding in these settings (light-moderate exercise, inactive/disease-burdened participants), however. Among sedentary men and women, Liepinsh et al. investigated respiratory function of PBMCs obtained 15 minutes following a one-hour bout of low-intensity (50 W, ~36% VO_{2max}) cycling exercise via Oxygraph (40). These authors observed increased routine OCR (+31%) in intact cells, as well as increased FA-dependent leak OCR (+65%), OXPHOS (+76%), and oxidative phosphorylation coupling efficiency (+22%) in permeabilized cells.

Cell Function: No reports investigated the effects of acute aerobic exercise of light-moderate intensity on cell function, in relation to cellular metabolism, in mixed cell populations among inactive participants and/or those with disease.

Isolated Cell Populations
No reports investigated the effects of acute aerobic exercise of light-moderate intensity on cellular metabolism and function in isolated cell populations among inactive participants and/or those with disease.

LIGHT-MODERATE INTENSITY AEROBIC EXERCISE: UNCATEGORIZED PARTICIPANTS

Bisset et al. investigated the effects of a short bout (3-4 minutes) of treadmill exercise on leukocyte respiration using a Warburg Respirometer (7). The exercise bout elicited an increase in systemic VO_2 (i.e., of the participants) of 8-49% versus pre-

exercise. In cells obtained 5 minutes post-exercise, the authors observed a 36-71% increase in leukocyte oxygen consumption. The health and activity characteristics of the participants related in the report were not clear, precluding aggregation with other reports of acute exercise.

Concurrent Exercise
No reports investigated the effects of acute exercise including both aerobic and resistance components on cellular metabolism and function in peripheral leukocytes.

Resistance Exercise
No reports investigated the effects of acute resistance exercise on cellular metabolism and function in peripheral leukocytes.

Effects of Chronic Exercise
Key findings regarding the effects of chronic exercise training on peripheral leukocyte metabolism and function are related in the following sections and in Table 7. These include results from both reports strictly investigating chronic exercise, as well as chronic exercise data from reports on the effects of both acute and chronic exercise. Unless otherwise noted, key findings refer to changes observed pre- to post-training in resting participants.

HEAVY-SEVERE INTENSITY AEROBIC EXERCISE TRAINING: ATHLETE PARTICIPANTS

Mixed Cell Populations
Metabolic Regulation: Two reports from the same author group investigated the effects of eight weeks of sport-specific training on PBMC metabolic regulation among male athletes (football/soccer) (12, 13). The authors observed increased Tfam, OPA1 dynamin like GTPase, and OMA1 zinc metallopeptidase protein expression in the first report (12). In the later report, increased mitochondrial uncoupling protein 2, mitochondrial uncoupling protein 3, COXIV and mitofusin 1, but decreased Tfam protein expression were observed (13). Additionally, no change in COXIV, PGC-1α, or mitochondrial NADH dehydrogenase subunit 5 mRNA expression was noted in this later report.

Metabolic Function: One study evaluated the effects of heavy-severe intensity training on metabolic function of mixed cell populations among athletes (27). Following three weeks of hypoxic sprint interval (SIH) or repeated sprint (RSH) cycling training in recreational athletes, the authors observed diminished PBMC ETS (RSH only) and PBMC ETS/citrate synthase activity (RSH & SIH) via Oxygraph. These results were obtained from only two participants per group and should be interpreted accordingly.

Cell Function: The two reports which investigated the effects of heavy-severe intensity aerobic exercise training on metabolic regulation also assessed the effects of training on cell function of PBMCs. In the earlier of the two reports, elevated PBMC protein carbonyls but decreased malondialdehyde levels were noted following the eight weeks of training (12). This suggests training altered redox balance in the cells. However, no change was observed in PMA-stimulated (10 ng/mL) H_2O_2 production. No change in PMA-stimulated (10 ng/mL) H_2O_2 production was also noted following training in the later report, as well as no difference in NF-κB activation versus pre-training (13).

Isolated Cell Populations
No reports investigated the effects of aerobic exercise training of heavy-severe intensity on cellular metabolism and function in isolated cell populations among athletes.

HEAVY-SEVERE INTENSITY AEROBIC EXERCISE TRAINING: HEALTHY ACTIVE PARTICIPANTS

Mixed Cell Populations
Metabolic Regulation: In the sole report of the effects of heavy-severe aerobic exercise training on metabolic regulation of mixed leukocyte populations in health active adults, Thomas et al. observed increased PBMC CD36 protein expression following eight weeks of continuous and interval-based cycling training (65). However, no significant change in PPARγ protein expression or in PPARγ phosphorylation was observed.

Metabolic Function, Cell Function: No reports investigated the effects of aerobic exercise training of heavy-severe intensity on metabolic function or cell function in mixed cell populations among healthy active participants.

Isolated Cell Populations
No reports investigated the effects of aerobic exercise training of heavy-severe intensity on cellular metabolism and function in isolated cell populations among healthy active participants.

HEAVY-SEVERE INTENSITY AEROBIC EXERCISE TRAINING: INACTIVE PARTICIPANTS AND/OR THOSE WITH DISEASE

Mixed Cell Populations
Metabolic Regulation: Two reports studied the effects of heavy-severe aerobic exercise training on metabolic regulation of mixed cell populations among inactive and/or participants with disease. Both reports observed minimal change in metabolic regulation of mixed leukocyte populations following training in inactive adults. After two weeks of HIIT by cycle ergometer, Hedges et al. noted no changes in PBMC PGC-1α, Tfam, nuclear respiratory factor 1, nuclear respiratory factor 2, or COXIV mRNA, or electron transport chain CI-CV protein expression (31). Similarly, six weeks of cycling HIIT did not change lymphocyte mitochondrial biogenesis proteins in the report from Tsai et al. (66). However, the latter authors did note declines in mitofusin and dynamin-related protein-1 (DRP-1). The greater relative decline in DRP-1 led to an increase in mitofusin:DRP-1 post-training versus pre-training, suggestive of increased mitochondrial fusion versus fission (66).

Metabolic Function: Four reports related data regarding the effects of heavy-severe aerobic exercise training on metabolic function in mixed cell populations in inactive individuals and/or those with disease. Three of these reports recruited sedentary but otherwise healthy males (17, 31, 66), and one report detailed the effects of exercise in women with systemic lupus erythematosus (23). Using Oxygraph, Chang and Wang (2015) observed increased ATP-linked OCR and decreased non-mitochondrial OCR in intact lymphocytes, and increased CI-linked OCR following six weeks of cycling HIIT (17). Tsai et al. also observed via Oxygraph increased ATP-linked OCR and Reserve OCR in intact lymphocytes following six

weeks cycling HIIT, as well as increased CII-linked OCR and OXPHOS of permeabilized cells, and increased succinate dehydrogenase activity (66). These authors also assessed the effects of acute hypoxic exercise (36 min, 100 W, 12% O2) following training and observed smaller exercise-induced depressions in lymphocyte OCR, and lactate dehydrogenase, succinate dehydrogenase, and citrate synthase activity (66). Contrary to the previous two reports, Hedges et al. noted no change in PBMC mitochondrial respiration (measured by Oxygraph) following two weeks HIIT despite improvements in mitochondrial respiration of permeabilized skeletal muscle fibers (31). Accordingly, skeletal muscle mitochondrial respiration was not correlated with PBMC respiration either pre- or post-training. Finally, Hasni et al. found an improvement in PBMC OCR:ECAR measured by Seahorse assay following 12 weeks treadmill exercise in women with systemic lupus erythematosus (29). Additionally, the change in OCR:ECAR was negatively correlated with change in self-reported fatigue (via Fatigue Severity Scale) ($r = -0.59$, $p = 0.03$) over the intervention (i.e., increase OCR:ECAR associated with decreased fatigue).

Cell Function: No reports investigated the effects of aerobic exercise training of heavy-severe intensity on cell function, in relation to cellular metabolism, in mixed cell populations among inactive participants and/or those with disease.

Isolated Cell Populations

Metabolic Regulation: Two reports presented data on the effects of heavy-severe aerobic exercise training on metabolic regulation in isolated cell populations in inactive individuals and/or those with disease. Bartlett et al. observed increased neutrophil MMP ($d = 1.10$) following ten weeks of treadmill HIIT in prediabetic overweight-obese older adults (6). Likewise, Lin et al. noted increased NK cell MMP at rest following six weeks of cycling HIIT in sedentary young males (41). The latter authors also observed smaller exercise-induced perturbations to NK cell MMP and mitochondrial oxidant burden (e.g., mitochondrial reactive oxygen species) in response to cycling GXT post-training (41).

Metabolic Function: The effects of heavy-severe intensity aerobic exercise training on metabolic function of isolated cell populations among inactive participants and/or those with disease were investigated in three reports. Following ten weeks of HIIT among adults afflicted with rheumatoid arthritis, Andonian et al. found via Seahorse assay that improvements in cardiorespiratory fitness positively correlated with post-training basal and maximal respiration of $CD4^+$ T cells ($\rho = 0.89$, $p = 0.019$ for both), and that improvements to CD4+ T cell mitochondrial respiration positively correlated with increases in CD4+ CCR7+CD45RA+ T cells (i.e., naïve cells) ($\rho = 0.89$, $p = 0.019$) (2). Among the cohort of prediabetic overweight-obese older adults discussed in the previous section, increased neutrophil basal respiration ($d = 3.01$), maximal respiration ($d = 2.86$), and ATP production ($d = 4.18$) were observed following training (measured by Seahorse assay) (6). Finally, using Oxygraph, Lin et al. noted increased NK cell ETS, Reserve OCR, and BHI at rest following six weeks HIIT in sedentary young male participants (41). These authors also found that the change in VO_{2max} pre- to post-training was positively correlated with pre- to post-training changes in ETS ($r = 0.549$, $p < 0.001$), Reserve OCR ($r = 0.655$, $p < 0.001$), and BHI ($r = 0.546$, $p < 0.001$).

Cell Function: Bartlett et al. and Lin et al. were the only groups to investigate the effects of heavy-severe intensity aerobic exercise training on cell function of isolated cell populations, in relation to cellular metabolism, among inactive participants and/or those with disease. The former group found improvements in a variety of measures of neutrophil function following training (Table 7), in parallel to the metabolic changes described in the previous sections (6). Notably, pre- to post-training changes in neutrophil chemotaxis were positively correlated with percent change in VO_{2peak} ($r = 0.649$, $p = 0.042$) and negatively correlated with change in relative body fat ($r = -0.721$, $p = 0.018$). These relationships suggest integration between systemic and cellular effects of HIIT training. In NK cells, Lin et al. noted increased perforin and granzyme b expression in unstimulated NK cells obtained from resting participants post-training (41). These functional changes complimented the training-related improvements in mitochondrial regulation and respiratory function previously described.

LIGHT-MODERATE INTENSITY AEROBIC EXERCISE TRAINING: ATHLETE PARTICIPANTS

No reports investigated the effects of aerobic exercise training of light-moderate intensity on cellular metabolism and function in peripheral leukocytes among athletes.

LIGHT-MODERATE INTENSITY AEROBIC EXERCISE TRAINING: HEALTHY ACTIVE PARTICIPANTS

Mixed Cell Populations

Metabolic Regulation: Only Morabito et al. investigated the effects of light-moderate aerobic exercise training on metabolic regulation of mixed cell populations in healthy active adults. These authors observed no changes in hypoxia inducible factor 1 subunit alpha (HIF-1α) mRNA expression or MMP of PBMCs obtained following ten days trekking at either low- (mean ± standard error of the mean (SEM): 598 ± 561m) or high-altitudes (4132 ± 863m) in the same participants (49). However, decreased mitochondrial ROS was noted following trekking at high-altitude.

Metabolic Function: In the same experiment discussed in the previous section, elevated PBMC metabolic activity (via staining with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT)) was observed following high-altitude but not low-altitude trekking (49).

Cell Function: Morabito et al. observed no change in unstimulated PBMC intracellular ROS or nitric oxide following either low- or high-altitude trekking (49).

Isolated Cell Populations

No reports investigated the effects of aerobic exercise training of light-moderate intensity on cellular metabolism and function in isolated cell populations among healthy active participants.

LIGHT-MODERATE INTENSITY AEROBIC EXERCISE TRAINING: INACTIVE PARTICIPANTS AND/OR

THOSE WITH DISEASE

Mixed Cell Populations

Metabolic Regulation: The effects of light-moderate aerobic exercise training on metabolic regulation of mixed leukocyte populations among inactive participants and/or those with disease were investigated in three reports. Implementing eight-week treadmill walking program among middle-aged (mean ± SD: 45.6 ± 11.1 years) adults, Butcher et al. observed increases in PBMC CD36 (mean ± SD: 3.86 ± 0.61-fold, 2.72 ± 0.53-fold) and PPAR (1.82 ± 0.89-fold, 4.27 ± 1.89-fold) mRNA expression at four and eight weeks of training versus pre-training or non-training participants (i.e., controls) (14). Increases in PBMC ABCA1 (3.46 ± 0.56-fold) and ATP-binding cassette subfamily G member 1 (ABCG1) (3.06 ± 0.47-fold) mRNA expression were also observed at eight weeks compared to pre-training or control participants. Similarly, Yakeu et al. noted increased PBMC PGC-1α (4-fold, 5-fold) and peroxisome proliferator-activated receptor α (PPARα) (1.6-fold, 1.6-fold) mRNA expression after four and eight weeks of training, and increased peroxisome proliferator-activated receptor γ coactivator 1-beta (PGC-1β) (2-fold) mRNA expression solely after eight weeks of treadmill training (73). Similar to HIIT, Tsai et al. found no change in lymphocyte mitochondrial biogenesis protein levels, and a decrease in mitofusin and DRP-1 following six weeks cycling moderate intensity continuous training (MICT) at 60% VO_{2max}(66). Unlike HIIT, the ratio of mitofusin to DRP-1 was not significantly altered via MICT (66).

Metabolic Function: Four reports related data on the effects of light-moderate intensity aerobic exercise on metabolic function of mixed cell populations among inactive participants and/or those with disease. Brand et al. observed increased lymphocyte OXPHOS (d = 1.27), ETS (d = 1.67), and CIV (d = 1.08) activity following 12 weeks training in men diagnosed with occupational burnout (10), as well as increased lymphocyte ATP content. Increased PBMC non-mitochondrial respiration (3.15-fold), maximal respiration (2.45-fold) and SRC (5.65-fold) were also observed by Kocher et al. following a twelve week training program in HIV+ men (36). Though, it should be noted the analytic platforms used in these two reports were not the same (Oxygraph-2k versus Seahorse XFe24, respectively). Therefore, the outcomes should not be interpreted as equivalent.

Finally, both Chang and Wang (2015) and Tsai et al. reported on the effects of cycling MICT at 60% VO_{2max} (17, 66). In the earlier of the two reports, Change and Wang observed increased lymphocyte ATP-linked OCR and decreased non-mitochondrial OCR in intact cells, as well as increased CII-linked OCR in permeabilized cells (17). The latter result contrasted with their participants that performed HIIT in whom increased CI-linked OCR was observed rather than CII. Tsai et al. also observed increased lymphocyte ATP-linked and Reserve OCR in intact cells following training, along with increased CII-linked OCR and OXPHOS in permeabilized cells, and increased succinate dehydrogenase activity (66). Finally, Tsai et al. also assessed the effects of acute exercise in hypoxia following training versus prior. Compared to pre-training, these authors observed smaller reductions in lymphocyte respiratory capacity, succinate dehydrogenase activity, as well as lactate dehydrogenase and citrate synthase activity due to hypoxic exercise (66). These trends were the same as those observed among their participants performing cycling HIIT rather than MICT. Both the reports of Chang and Wang and Tsai et al. utilized the same analytic platform (Oxygraph-2K) for measuring metabolic function.

Cell Function: No reports investigated the effects of aerobic exercise training of light-moderate intensity on cell function, in relation to cellular metabolism, in mixed cell populations among inactive participants and/or those with disease.

Isolated Cell Populations

Metabolic Regulation: One report investigated the effects of light-moderate intensity aerobic exercise training on metabolic regulation (as well as metabolic function and cell function) in isolated cell populations among inactive participants and/or those with disease. As they did with their participants performing HIIT, Lin et al. found increased NK cell mitochondrial content and MMP, and decreased mitochondrial oxidant burden following six weeks of cycling MICT at 60% VO_{2max} (41). Notably, GXT post-training also led to smaller reductions in mitochondrial count and membrane potential, as well as smaller increases in mitochondrial oxidant burden versus GXT pre-training.

Metabolic Function: Lin et al. also observed increased ETS, Reserve OCR and BHI of NK cells, and a positive correlation between change in participant VO_{2max} versus change in the latter measures of NK cell respiratory function (ΔVO_{2peak} vs. ETS $r = 0.549$, $p < 0.001$; ΔVO_{2peak} vs. Reserve OCR $r = 0.655$, $p < 0.001$; ΔVO_{2peak} vs. BHI $r = 0.546$, $p < 0.001$) as measured by Oxygraph (41). These trends were the same as those observed among participants in the study performing HIIT rather than MICT.

Cell Function: In the same report discussed in the previous two sections, unstimulated NK cell perforin and granzyme b were found higher post-training versus pre-training and this result was the same as what was observed among participants that completed HIIT (41).

Concurrent Exercise Training: Athlete Participants or Healthy Active Participants

No reports investigated the effects of concurrent exercise training on cellular metabolism and function of peripheral leukocytes among athletes or healthy active participants.

Concurrent Exercise Training: Inactive Participants and/or Those with Disease

Mixed Cell Populations

Metabolic Regulation: Lehti et al. were the sole report on the effects of concurrent exercise training (38). As assessed by microarray, these authors recorded increased PBMC expression of oxidative phosphorylation genes ($z = 3.27$) among those participants that improved VO_{2max} following 21 weeks of training (n=7). All participants, both those included the gene expression sub-study and those not included, were sedentary adults with stable coronary artery disease.

Metabolic Function or Cell Function: No reports investigated the effects of concurrent exercise training on metabolic function or cell function, in relation to cellular metabolism, in mixed cell populations among inactive participants and/or those with disease.

Isolated Cell Populations
No reports investigated the effects of concurrent exercise training on cellular metabolism and function in isolated cell populations among inactive participants and/or those with disease.

RESISTANCE EXERCISE TRAINING: ATHLETE PARTICIPANTS
No reports investigated the effects of resistance training on cellular metabolism and function in peripheral leukocytes among athletes.

RESISTANCE EXERCISE TRAINING: HEALTHY ACTIVE PARTICIPANTS

Mixed Cell Populations
Metabolic Regulation: One report related data on the effects of resistance training on leukocyte metabolic regulation (21). Among healthy active older adults (mean ± SEM: 73.7 ± 2.2 years) randomized to eight weeks of resistance training, increased PBMC PGC-1α and mitofusin 1 protein expression were observed post- versus pre-training. Mitofusin 1 expression post-training among trained participants was also greater than in the control group.

Metabolic Function or Cell Function: No reports investigated the effects of resistance training on metabolic function or cell function in mixed cell populations among healthy active participants.

Isolated Cell Populations
No reports investigated the effects of resistance training on cellular metabolism and function in isolated cell populations among healthy active participants.

RESISTANCE EXERCISE: INACTIVE PARTICIPANTS AND/OR THOSE WITH DISEASE

No reports investigated the effects of resistance training on cellular metabolism and function in peripheral leukocytes among inactive participants and/or those with disease.

Effects of Physical Fitness
Key findings regarding the effects of physical fitness on peripheral leukocyte metabolism and function are related in the following sections and in Table 8. These include results from reports strictly investigating physical fitness, as well as physical fitness data from reports on the effects of both physical fitness and acute exercise. Unless otherwise noted, key findings refer to differences observed between participant fitness classes in samples obtained from resting participants. Categorization by exercise intensity/type and participant population is not performed in this section due to the inclusion of multiple participants populations and a lack of acute or chronic exercise in these reports.

Mixed Cell Populations
Metabolic Regulation: Two reports compared metabolic regulation of mixed cell populations between participants varying in physical fitness. In lymphocytes, Dorneles et al. observed greater mitochondrial membrane depolarization of cells from low-fitness participants (mean ± SD: 38.1 ± 1.7 mL/kg/min. VO_{2peak}) versus cells of those in the moderate-fitness (43.9 ± 2.7 mL/kg/min. VO_{2peak}) and high-fitness groups (55.1 ± 4.7 mL/kg/min.VO_{2peak}) when stimulated with 10 μg/mL Con-A (20). No differences in mitochondrial membrane polarization were observed among unstimulated and 5 μg/mL Con-A stimulated lymphocytes. Mota et al. also noted differences in mitochondrial ROS production in their report comparing men of lower versus higher cardiorespiratory fitness across three age-groups (19-29 years mean ± SD: 42.9 ± 5.1 vs. 57.4 ± 3.9 ml/kg/min. VO_{2max}, 30-39 years 38.5 ± 1.9 vs. 51.3 ± 3.3 mL/kg/min. VO_{2max}, 40-59 years 33.9 ± 5.5 vs. 49.1 ± 5.5 mL/kg/min. VO_{2max}) (50). Compared to the men of higher fitness in each age-group, unstimulated lymphocytes of men in the lower fitness group demonstrated greater mitochondrial H_2O_2 production (50).

Metabolic Function: Metabolic function was the most studied outcome area in reports investigating the effects of physical fitness on mixed cell populations, with six reports retrieved. Vladutiu et al., measuring oxidation of radiolabeled palmitic acid in whole blood, found greater FA oxidation in leukocytes of endurance-trained runners (central tendency not reported: 47.9 mL/kg/min. VO_{2peak}) and sedentary women (34.3 mL/kg/min. VO_{2peak}) versus three female siblings with genetic deficiency for the FA transporter carnitine palmitoyltransferase 2 (CPT2) (36.5, 39.5, and 43.6 mL/kg/min. VO_{2peak}) (69). Greater leukocyte FA oxidation was also observed among the endurance trained versus sedentary women, and a positive correlation was found between leukocyte FA oxidation versus VO_2 achieved at an RER of 1.0 during GXT (r = 0.94, p-value not reported). In a later report also evaluating leukocyte FA oxidation by the same technique, inactive participants (male and female) and non-elite athletes (runners) did not differ, nor did leukocyte FA oxidation differ between inactive participants and those afflicted with a variety of diseases (Table 8) (53). The notable exception in this regard was that of participants with chronic fatigue syndrome, whose values for leukocyte FA oxidation exceeded those of the untrained. Leukocyte FA oxidation of elite athletes (endurance runners) was greater than that of non-elite athletes and the inactive, and FA oxidation of females with genetic deficiency in CPT2 (two of the aforementioned 3 siblings) was less than all other groups (53).

In their comparison of lymphocyte metabolic function across age and fitness, Mota et al. measured lymphocyte oxygen utilization polarographically by a Clarke electrode. The authors report greater CI activity among lower fitness individuals in the 19-29 and 30-39 years age-groups compared to those of higher fitness at each age (50). No difference in CI activity was observed between fitness levels in the 40-59 years age-group. Additionally, a negative correlation was noted between lymphocyte CI activity versus age (i.e., decline in CI activity with advancing age) (r = -0.472, p-value not reported) only among those of lower fitness (50). Tyrell et al. also observed relationships between physical fitness and leukocyte respiratory function (Seahorse assay) in the context of aging (67). Among a cohort of overweight and obese older adults (65-79 years), positive correlations were found between PBMC maximal OCR and SRC versus various measures of physical fitness and body composition (Table 8). A positive correlation was also observed between PBMC basal OCR versus knee extensor maximal

strength (r = 0.51, p < 0.05), and negative correlations were observed between PBMC basal OCR (r = -0.61, p < 0.05), maximal OCR (r = -0.58, p < 0.05), and SRC (r = -0.55, p < 0.05) versus plasma IL-6 (67). In contrast to the results of the latter two reports, Farinha et al. observed no differences in mitochondrial or non-mitochondrial metabolic activity of PBMCs of healthy active (mean ± SD: 22.22 ± 4.67 mL/kg/min. VO_{2max}) versus inactive (18.6 ± 2.01 mL/kg/min. VO_{2max}) postmenopausal women (22). These conclusions were based on PBMC CI and CII activity, and MTT staining.

Janssen et al. were the only report to assess the effects of physical fitness in both stimulated and unstimulated mixed cells (34). Using the Seahorse Assay, in unstimulated PBMCs, these authors noted greater values for various measures of mitochondrial respiratory function among participants (females only) of high fitness (median: 50.4 mL/kg/min. VO_{2peak}) versus those of low-fitness (median: 35.1 mL/kg/min. VO_{2peak}), but no differences in glycolytic function between groups (34). Stimulation with Con-A (25 μg/mL) increased mitochondrial respiration and glycolysis in both groups. However, Con-A-stimulated basal and maximal OCR of PBMCs from high-fitness participants was greater than those of the low-fitness participants (34). Glycolytic function in Con-A-stimulated PBMCs did not differ between the groups.

Cell Function: Differences in cell function of mixed cell populations relative to physical fitness were reported among both young male and postmenopausal female participants. Among young male participants, Dorneles et al. found that unstimulated and 5 μg/mL Con-A-stimulated lymphocytes from lower-fitness participants produced greater ROS than moderate-fitness and high-fitness participants (20). However, no differences in ROS production were observed between groups when cells were stimulated with 10 μg/mL Con-A (i.e., highest concentration). Unstimulated and 5 μg/mL stimulated lymphocytes from high-fitness participants also demonstrated lower proliferation than cells of the moderate-fitness and low-fitness groups, with no group differences in proliferation observed following stimulation with 10 μg/mL Con-A (20). In contrast to these results, Farinha et al. observed unstimulated ROS production of PBMCs from healthy active postmenopausal women to be greater than that of inactive women (22). However, superoxide dismutase and catalase activity were also greater in cells from healthy active women versus the inactive, and this elevated antioxidant activity may have provided some protection from elevated ROS in the active women.

Isolated Cell Populations

Metabolic Regulation: Antunes et al. and Alley et al. were the only two reports to assess the effects of physical fitness on metabolic regulation of isolated leukocyte populations. In monocytes isolated from PBMCs by tissue-culture adherence, Antunes et al. observed greater LPS-stimulated (100 ng/mL) PPARγ mRNA among participants of high-fitness (mean: 63.1 mL/kg/min. VO_{2max}) versus those in the low-fitness group (35.3 mL/kg/min. VO_{2max}) (3). The authors also noted greater PGC-1α mRNA expression in cells from high-fitness participants under all treatment conditions (LPS 100 ng/mL, rosiglitazone 1 μM, LPS 100 ng/mL + rosiglitazone 1 μM) (group effect $\eta_2 = 0.513$). However, greater AMPK mRNA expression was observed under all treatment conditions in cells of the low-fitness group (group effect $\eta_2 = 0.372$).

Relationships between physical fitness and metabolic regulation in naïve CD8+ and CD4+ T cells were evaluated in the report from Alley et al. (1). In this report, flow cytometric analyses of mitochondria allowed assessment of T cell populations within the PBMC pool. Naïve CD8+ T cells from participants in the high-fitness group (mean ± SD: 59.6 ± 9.0 mL/kg/min. VO_{2peak}) exhibited greater mitochondrial mass than cells of the inactive group (42.7 ± 7.4 mL/kg/min. VO_{2peak}) (d = 0.76). However, the groups were not different in MMP and mitochondrial biogenesis of naïve CD8+ or CD4+ T cells. Positive correlations among all participants were noted for both mitochondrial mass of naïve CD4+ and CD8+ T cells versus estimated participant energy expenditure (r = 0.41, p = 0.024 and r = 0.36, p =0.048), and for mitochondrial mass of naïve CD8+ T cells versus VO_{2peak} (r = 0.47, p = 0.009) (1). A negative correlation was observed for naïve CD8+ T cell mitochondrial mass versus percent body fat (r = -0.43, p = 0.017) as measured by bioelectrical impedance analysis. Sex and body composition appear to be important factors in the previous relationships because correlations between T-cell mitochondrial mass and estimated energy expenditure or VO_{2peak} were no longer significant when controlling for percent body fat. Similarly, correlations between T-cell mitochondrial mass and estimated energy expenditure were no longer significant when controlling for sex (1). However, the positive relationship between CD8+ mitochondrial mass and VO_{2peak} remained significant (r = 0.42, p =0.024).

Metabolic Function: In the previously mentioned report, Alley et al. also isolated naïve CD8+ T cells from PBMCs by immunomagnetic bead separation. They found no differences in glycolytic or mitochondrial function of anti-CD3/anti-CD28 co-stimulated naïve CD8+ T cells from participants in their high-fitness versus low-fitness groups, as measured by Seahorse assay (1).

Cell Function: Antunes et al. were the sole report to assess the effects of physical fitness on cell function of isolated leukocyte populations. In this report, monocytes from participants in their low-fitness group demonstrated greater LPS-stimulated (100 ng/mL) IL-10 production versus monocytes from those in the high-fitness group (3).

DISCUSSION

Overview

Research in the past two decades has demonstrated the integral role of cellular metabolism in directing immune cell phenotype and function. Furthermore, there are accumulating data from the field of exercise immunology revealing the ways exercise affects immune function via cellular metabolism. Given this context, the current review aimed to set a foundation for future work by summarizing the current body of literature regarding the effects of exercise and physical fitness on leukocyte energy metabolism. Figure 2 summarizes the number of studies that have been performed within different participant populations and by different experimental designs (e.g., acute exercise, physical fitness comparisons). The volume, breadth, and timespan of reports uncovered in the review were surprising

and suggest early and persistent interest in the metabolic effects of exercise on immune cells. However, while the diversity of reports provides an extensive resource to inspire additional research, it also presents some limitations to interpretation.

Limitations

The limitations of the literature are apparent when one attempts to reconcile the data against the heterogeneity of sample populations, types of exercise and/or training implemented, timepoints of blood collection in relation to exercise, and measurement techniques. We have attempted to resolve this heterogeneity by organizing the data based on exercise type and intensity, participant population, cell populations, and outcomes. The strength of this approach is that it efficiently reveals gaps in the literature; particularly regarding the effects of concurrent and resistance training. However, this organizational strategy in some cases may be incomplete, and all reports within a category may not provide appropriate comparisons. This strategy was chosen to find balance between organizational structure and dividing the dataset into sections too small for meaningful comparison. Given the objective of scoping reviews to be mainly descriptive (4, 56), the balance was weighted towards larger categories for the purpose of summary and comparison. However, we understand the diverse nature of the literature means our approach may not fit all aspects of the dataset equally and this remains a limitation of the review.

Additional limitations of the review include the possibility of missing reports and no weight of results relative to study quality. The first limitation is a consequence of methodological choices in the execution of the review. We attempted to cover a wide swath of the biomedical literature through our choice of databases. Nevertheless, it is possible relevant literature remain outside the reach of our search methods and therefore were not included in the review. This leaves the door open for future reviews to build on the current work. Also, though useful in weighing evidence between reports, critical analysis of study quality is not within the purview of scoping reviews and was therefore not implemented in this one. We encourage future systematic reviews and meta-analyses to implement such assessments to provide further clarity of research findings.

Acute Exercise Data

Despite the above-mentioned limitations of the current literature and this review, noteworthy trends and knowledge gaps were observable in the data. These results should offer direction for future research that we will now discuss.

Trends

Heavy-Severe Intensity Aerobic Exercise

Acute aerobic exercise of heavy-severe intensity was associated with changes in the expression of genes related to nutrient acquisition and mitochondrial respiration, including mitochondrial biogenesis. In general, increased gene expression was observed post-exercise. However, the timepoint of blood sampling appears important as positive results were more frequently observed in samples obtained >2h post-exercise. These trends were observed among athletes in mixed cell populations, and among healthy active participants in both mixed and isolated cell populations. In contrast, inconsistent results were observed regarding the effects of heavy-severe exercise on protein expression. This inconsistency may be attributable to the relatively fewer reports that assessed protein versus gene expression, or specifics of the participants and the exercise bout. Though the lone report to investigate the effects of acute heavy-severe aerobic exercise on metabolic regulation in inactive participants did not assess gene or protein expression, they did measure effects on mitochondria. Their observations that acute exercise increased the mitochondrial oxidant burden of NK cells, but did not alter mitochondrial count or MMP, implies that mitochondrial oxidative stress is a consequence of heavy-severe exercise among inactive participants (41).

Data obtained in athletes, healthy active, and inactive participants indicate acute heavy-severe intensity aerobic exercise alters peripheral leukocyte metabolic function. These changes were observed in both mixed cell populations, in monocytic cells incubated with post-exercise plasma in vitro, and in NK cells. However, it remains unclear whether observed changes in enzyme activity and substrate oxidation simply reflect shifts in substrate use versus change in total cellular metabolic activity. Furthermore, three reports suggest that exercise-induced changes in metabolic function may be due to exercise-induced changes in peripheral cell counts versus within-cell changes (44, 53, 64). These results were not observed in all reports, however, and it remains possible that within-cell changes may occur differentially between cell types. The report of Lin et al. provides some information to both of these questions, as increased ETS and Reserve OCR were observed post-exercise in NK cells (41). This implies NK cells are metabolically sensitive to acute exercise in sedentary men. Whether similar responses are observed in other cell types or participant populations remains to be determined.

Few reports investigated cell function in the context of acute heavy-severe aerobic exercise. Data from Busquets-Cortes et al. indicate increased stimulated intracellular ROS production in PBMCs alongside increased markers of mitochondrial regulation post-exercise (13). Further, Lin et al. report that exercise increased cytolytic mediators by NK cells alongside increased mitochondrial oxidative burden and increased ETS and Reserve OCR (42). However, the data are conflicted as to whether heavy-severe exercise has a stimulatory or inhibitory effect on measures of cell function, as lowered cell function is also reported (26, 49). Resolving this conflict will be important to determine whether exercise-induced changes in metabolic regulation and function, such as those described, imply promotion or suppression of immune function.

Light-Moderate Intensity Aerobic Exercise

Few reports investigated the effects of acute light-moderate aerobic exercise, and inactive participants with or without an ongoing disease were the only participant population studied. This perhaps is not surprising, given light-moderate exercise may be expected to deliver insufficient physiological stress to observe effects among healthy active participants or athletes. However, given the lack of data, whether this assumption is true remains unclear. Among inactive participants with or without disease, acute exercise was associated with depressed signaling for mitochondrial biogenesis, and mixed effects on mitochondrial regulation. However, unfortunately, methodological choices in the latter investigations direct that these results be interpreted with caution. Blood samples were acquired thirty minutes post-exercise in the report from Ferrer et al. (23), which the data on heavy-severe exercise suggests is too soon to observe

effects on PBMC gene expression. Additionally, though moderate, exercise in the reports from Tsai et al. and Chang and Wang was performed in hypoxic conditions (16, 66). Thus, the physiological stress of the bout was likely in excess of the moderate cycling workloads and therefore may not faithfully reflect the effects of moderate intensity cycling on PBMCs and lymphocytes.

Knowledge Gaps Regarding Acute Exercise

Major knowledge gaps regarding the effects of acute exercise on peripheral leukocyte metabolism and function include: effects of concurrent and resistance training, effects on glycolytic function, changes in substrate use versus overall metabolic rate, the influence of exercise intensity within individuals and between cell types. It is striking that no reports tested the effects of acute concurrent or resistance training bouts. These are major gaps in the literature that deserve attention due to the unique benefits each type of exercise offers. Additionally, few of the included reports assessed changes in the regulation or function of glycolysis. Given the dramatic changes in oxygen consumption and substrate utilization during acute exercise, and the role of glycolysis in facilitating immune cell activation, evaluating the regulation of glycolysis in leukocytes with exercise will be worthwhile. Related, evaluating activity of specific metabolic pathways in parallel with overall metabolic rate (e.g., oxygen consumption, ATP production) will be useful towards understanding if exercise only shifts leukocyte substrate use and/or alters metabolic rate. Such information will inform strategies (e.g., immunonutrition) to support immune function in the context of exercise or occupational physical activity. Finally, it is essential to resolve the effects of acute exercise on leukocyte metabolic function relative to exercise intensity and cell proportions. Contrasting the effects of variable exercise intensity within individuals, as well as between mixed versus isolated cell types, will help contextualize previous results and suggest if and how acute exercise can be used to modulate immunometabolism. These data will be instrumental to determining which cell types may be most metabolically sensitive to exercise and the immunometabolic effects imposed at different intensities.

Chronic Exercise Data

Trends

Heavy-Severe Intensity Aerobic Exercise

Heavy-severe aerobic exercise training was associated with changes in the expression of proteins regulating cellular metabolism in athletes and healthy active participants, but not sustained changes in gene expression. Among athletes, training led to increased expression of proteins that suggest signaling for mitochondrial biogenesis in mixed cell populations. Heavy-severe training in healthy active participants also led to increased protein expression, but for FA transport rather than mitochondrial biogenesis. The latter data stem from only one report, however, and therefore remain to be replicated for confirmation. In contrast to data obtained from athletes and healthy active participants, minimal changes in gene or protein expression of mixed cell populations were observed among inactive participants with or without disease following training. However, the change in ratio of mitochondrial dynamics proteins in one report imply increased mitochondrial fusion (66). In isolated cells, elevated MMP was noted post-HIIT training in two reports, alongside evidence for improved redox regulation (41). Taken together, the available data suggest heavy-severe aerobic exercise training signals for changes in mitochondrial homeostasis among mixed and isolated cells that may improve mitochondrial redox regulation. Though, training periods of six weeks or greater appear required to observe such changes.

The majority of data regarding the effects of heavy-severe aerobic exercise training on metabolic function were collected among inactive participants with or without disease, with too few results in athletes or healthy active participants for further commentary (Figure 2). In sum, data among inactive participants with or without disease indicate heavy-severe aerobic exercise training results in improvements to oxidative phosphorylation and respiratory capacity of peripheral leukocytes. Similar results were observed in both mixed cell population and isolated cell types; including T cells, neutrophils, and NK cells. However, data indicate that training must be in excess of two weeks to observe respiratory adaptations, as one report that only instituted a two-week training program observed no significant improvements to PBMC respiration (31). These trends are promising given the parallels to adaptations documented in skeletal muscle, and the importance of mitochondrial function to immune function (46).

Similar to the data on metabolic function, few reports assessed the effects heavy-severe aerobic exercise training on cell function. The two reports which investigated cell function following training in athletes observed minimal evidence of functional changes at rest in PBMCs, despite evidence of mitochondrial biogenesis signaling at the protein level (12, 13). In contrast, data obtained in inactive participants with or without disease indicate HIIT training can lead to improvements in cell function of both neutrophils and NK cells (6, 41). Notably, cell functional changes occurred alongside improvements to both cardiorespiratory fitness and cellular respiratory capacity, implying coordinated metabolic adaptation to exercise training.

Light-Moderate Intensity Aerobic Exercise

No reports investigated light-moderate training among athletes and only a single report on light-moderate aerobic exercise training in healthy active participants was recovered. The data of this latter report suggest light-moderate training is insufficient to alter cellular metabolism of lymphocytes, unless additional stimuli are provided (e.g., hypobaric hypoxia) (49). Though, these results deserve replication for confirmation given the limited data. In contrast, reports among inactive participants with or without disease were relatively more numerous. In mixed cells, greater expression of genes regulating lipid transport and oxidation were observed following training in two reports (14, 73), and decreased expression of proteins regulating mitochondrial dynamics were noted in one report (66). In isolated cells, training led to improvements in measures of mitochondrial function, both at rest and following acute heavy-severe intensity exercise (41). Together, the data indicate light-moderate training alters nutrient acquisition and mitochondrial homeostasis of peripheral leukocytes, with the potential for improved resilience to stresses such as exercise.

Data obtained in both healthy active and inactive participants with or without disease indicate light-moderate training can result in improvements in metabolic function of both mixed and isolated cell populations. Improvements in various markers of cell respiratory function were observed following training in lymphocytes of men diagnosed with occupational

burnout (10), in PBMCs of men with HIV (36), and in PBMCs, lymphocytes, or NK cells of sedentary but otherwise healthy young men (17, 41, 66). Two of these reports are notable for their investigations of acute exercise effects following training. Those data, obtained in one case in lymphocytes and in the other in isolated NK cells, indicate training-related changes mitigate the metabolic perturbations induced by acute exercise of peripheral lymphocytes (41, 66).

Only a single report was retrieved which evaluated the effects of light-moderate aerobic exercise training on cell function (41). These data were obtained in isolated NK cells and indicate light-moderate training may elicit equivalent changes in cell function as heavy-severe aerobic exercise training. Increased levels of granzyme b and perforin were recorded in NK cells of participants that completed light-moderate MICT or HIIT in this report, without differences between the groups. These results are promising and suggest light-moderate training may be sufficient stimulus to improve immune cell function among sedentary individuals. However, given this is but a single report, they also deserve follow up to determine the minimal as well as maximal effective intensities of aerobic exercise training in regard to peripheral leukocyte metabolism and function.

Knowledge Gaps Regarding Chronic Exercise

Despite revealing a number of trends worthy of comment, review of the data regarding the effects of exercise training on leukocyte metabolism and function also uncovered numerous gaps in knowledge. The most notable of these gaps include: the effects of concurrent and resistance training, the effects of training on different cell types obtained from the same participants, and the effects of exercise training on cellular glycolysis. Few reports investigated concurrent or resistance training at all, much less at different intensities, in different populations or cell types (Figure 2). Further, only a single study with healthy active participants employed a heavy-severe intensity training program, which might be expected to have a greater impact on cell metabolism and function. Although, this remains to be determined. The available data indicates these training styles are safe in both inactive and healthy participants, with promising results regarding metabolic regulation. Consequently, it will be important for future work to extend these studies to other populations (e.g., athletes), outcomes (metabolic function, cell function), and cell types to characterize the immunometabolic effects of resistance and the combination of aerobic and resistance exercise.

It also remains unclear how a given training program differentially affects various cells within the peripheral leukocyte pool. It is clear that metabolic differences exist between cell types and activation states (52, 59). However, whether differences also exist between cell types in regard to exercise and training remains unclear. Consequently, prospective comparisons of exercise training effects between different cell types will be extremely valuable for interpreting results coming from mixed populations and ascertaining whether certain cells are more or less "trainable." Finally, scant data were recovered concerning the effects of exercise training on leukocyte glycolytic function. As was stated previously when discussing acute exercise, glycolysis is integral to leukocyte activation and pathogen control, but is likewise linked to inflammation. Therefore, whether training improves or suppresses glycolytic function will have important implications toward the potential benefits and harms of pursuing exercise. In some cases, increasing cell activation and inflammatory potential may be helpful (e.g., recovering from sepsis), while in others it may be detrimental (e.g., chronic inflammatory disease). However, without knowledge of the effects of exercise training on leukocyte glycolysis it will be difficult to forecast its costs versus benefits.

Physical Fitness Data

Trends

Given the comparative methodological burden of acute exercise and training interventions, it was surprising that fewer cross-sectional reports on physical fitness were retrieved (Figure 2). Yet, the lack of reports leaves the door open for additional research and invites study of the relationships between physical fitness and leukocyte metabolism among many populations of interest. For example, no studies examined effects of physical fitness on metabolic regulation within populations with disease (Figure 2). With the caveat that there were relatively few data to draw upon, available data indicate higher fitness is associated with more stable mitochondrial function, greater substrate oxidation and respiratory enzyme activity among mixed cell populations. In parallel to these metabolic differences, cells of fitter individuals may also exhibit lower basal ROS production and proliferation, without compromised ROS and proliferation with maximal activation. Among isolated cell types, the data demonstrate positive associations between host fitness and signaling for lipid metabolism and mitochondrial biogenesis in monocytes (3), as well as mitochondrial mass in naïve T cells (1).

Knowledge Gaps Regarding Physical Fitness

A worthwhile avenue for future research will be defining the contexts in which differences in leukocyte metabolism present relative to physical fitness. Investigating individuals across the fitness continuum is an important aim to define if and how leukocyte metabolism scales with fitness and health. The thresholds of fitness for observing cellular differences may vary by health and activity status. Therefore, studies in diverse participant populations will provide context for interpreting the implications of leukocyte metabolism relative to fitness. It will also be valuable to document relationships between systemic and cellular metabolism of individuals of similar fitness, but differing in age or sex, and comparing cell types. Such data will inform how age- and sex-related effects change the latter relationships, and if the strength of relationships between systemic and cellular metabolism vary between leukocyte types. Finally, as was also true for acute exercise and chronic exercise, few studies of physical fitness assessed cell function alongside cell metabolism. Therefore, the impact of fitness-based differences in leukocyte metabolic regulation and function toward defense against pathogens and malignant cells remains opaque. Of all objectives, linking systemic and leukocyte metabolism with immune function may be the most important in regard to host health. We strongly recommend future investigations integrate measures of immune cell function (e.g., pro-/anti-inflammatory cytokine production, cytotoxicity) alongside metabolic assessments to situate cellular metabolic data relative to immune function and host health.

SUMMARY AND CONCLUSION

Effectively engaging cellular metabolic pathways is essential

to both exercise performance and immune function. Given the beneficial effects of exercise on systemic and skeletal muscle metabolic function, and on immunity, the potential for exercise to modulate immune function via leukocyte metabolism seems a logical possibility. The current literature suggest acute exercise can influence the regulation of leukocyte energy metabolism and metabolic function, and that the stimuli of training may enhance metabolic capacity (e.g., enhanced maximal oxidative phosphorylation capacity). However, there remain notable gaps in the literature to be filled with future research. These gaps include the effects of exercise and fitness on leukocyte glycolytic function, intensity and duration thresholds for exercise-induced leukocyte metabolic adaptations, as well as the existence and magnitude of differences in the metabolic response to exercise between cell types and subsets. In addition, relatively few studies examined cell function concurrently with measures of metabolic regulation or metabolic function. Ideally, future studies investigating acute and chronic exercise effects on cellular metabolism will include data on the regulation of cellular metabolism (e.g., protein expression, mitochondrial dynamics), metabolic function (e.g., mitochondrial respiration), as well as cell function (e.g., stimulated proliferation, cytokine production) to characterize the immediate and adaptive consequences of exercise and training. Such data will improve understanding of whether and how exercise affects immune function via cellular metabolism and inform the application of acute and chronic exercise to support both immune function and systemic health and well-being.

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Author, year	Table 2: Report Characteristics - Effects of Acute Exercise					
	Exercise Type and Intensity; Session	**Participants**	**Cell Population; Sampling Time Point**	**Participant Characteristics (N, % male, age)**	**Participant BMI, Body Composition**	**Fitness Assessment; Participant Fitness**
Capo X et al., 2020[b,c] (15)	Aerobic, heavy-severe intensity; 5 min. each @ running speed corresponding to 50%, 60%, 70% VO_{2max}, anaerobic threshold (to exhaustion)	Athletes (professional taekwondo)	PBMCs; Pre- vs post-exercise (2h)	11, 100%, N/R	N/R	VO_{2max} via treadmill GXT; mean ± SEM: 46.1 ± 4.8 ml/kg/min.
Ferry A, Marsac C, Duvallet A, Rieu M, 1991 (24)	Aerobic, heavy-severe intensity; Same as fitness test (i.e., treadmill GXT)	Athletes (endurance sports)	PBMCs; Pre- vs post-exercise	6, N/R, mean ± SD: 29.3 ± 2.0 y/o	N/R	VO_{2max} via treadmill GXT; mean ± SD: 68.7 ± 1.3 ml/kg/min.
Hunter DJ et al., 2019[b] (33)	Aerobic, heavy-severe intensity; 45 min. @ 70% W_{max} then 15 min. time-trial	Athletes (trained cyclists)	PBMCs; Pre- vs post-exercise	8, 100%, mean ± (error type unspecified): 39.50 ± 5.9 y/o	N/R	VO_{2max} via cycle ergometer GXT; mean ± (error type unspecified):53.88 ± 5.24 ml/kg/min.
Nieman DC et al., 2018[b] (51)	Aerobic, heavy-severe intensity; 75km indoor cycling time-trial	Athletes (trained cyclists)	Plasma; Pre- vs post-exercise (0 h, 0.75 h, 1.5 h, 3 h, 4.5 h, 21 h, 45 h post-exercise)	All: 20, 70%, N/R; mean ± SEM: F: 43.7 ± 2.2 y/o M: 37.1 ± 2.5 y/o	F: N/R, 18.8% BF M: N/R, 19.5% BF	VO_{2max} via cycle ergometer GXT; mean ± SEM: F: 46.5 ± 2.8 ml/kg/min., M: 47.0 ± 1.5 ml/kg/min.
Davies NA et al., 2015[b] (18)	Aerobic, heavy-severe intensity; 45 min. @ 70% VO_{2max}	Healthy, Active	PBMCs; Pre- vs post-exercise (0 h, 1.5 h, 3 h, 24 h post-exercise)	5, 100%, mean ± SD: 32 ± 8 y/o	N/R	VO_{2max} via cycle ergometer GXT; mean ± SD: 44 ± 14 ml/kg/min.
Frisina JP et al., 1994 (26)	Aerobic, heavy-severe intensity; 25 x 1 min. @ 112% maximal GXT pace, 2 min. rest	Healthy, Active	PBMCs; Pre- vs post-exercise	7, 100%, mean ± SD: 21.7 ± 1.3 6y/o	N/R	GXT to exhaustion via treadmill; N/R
Moir H et al., 2010 (48)	Aerobic, heavy-severe intensity; 45 min. cycling/running @ 70% VO_{2max}	Healthy, Active	PBMCs; Pre- vs post-exercise (0h, 1h)	Cycling: 16, 100%, mean ± SD: 23.1 ± 0.5 y/o Running: 8, 100%, 21.1 ± 1.2 y/o (subset of 16)	N/R	VO_{2max} via cycle ergometer GXT; mean ± SD: 56.3 ± 1.1 ml/kg/min.
Moir et al., 2008 (47)	Aerobic, heavy-severe intensity; 45 min. cycling @ 70% VO_{2max}	Healthy, Active	PBMCs; Pre- vs post-exercise (0 h, 1 h)	10, 100%, mean ± SD: 23.1 ± 0.5 y/o	N/R	VO_{2max} via cycle ergometer GXT; mean ± SD: 56.6 ± 1.1 ml/kg/min.
Theall B et al., 2021 (64)	Aerobic, heavy-severe intensity; 30 min. cycling @ watts corresponding to 65-75% VO_{2peak}	Healthy, activity N/R	PBMCs & T cells[d]; Pre- vs post-exercise	All: 21, 57%, mean ± SD: 27.0 ± 5.4 y/o F: 24.0 ± 3.9 y/o M: 29.3 ± 5.4 y/o (significantly different from F)	All: mean ± SD: 25.8 ± 4.0 kg/m^2; N/R F: 24.4 ± 2.9 kg/m^2; N/R M: 26.8 ± 4.5 kg/m^2; N/R (sig. different from F)	VO_{2peak} via cycle ergometer GXT; All: mean ± SD: 36.5 ± 6.3 ml/kg/min. F: 36.8 ± 3.1 ml/kg/min. M: 36.3 ± 8.1 ml/kg/min.
Meksawan K et al., 2005[b] (44)	Aerobic, heavy-severe intensity; Same as fitness assessment (i.e., treadmill GXT)	Healthy, Inactive	Leukocytes in whole blood; Pre- vs post-exercise	All: 10, 40%, N/R mean ± SEM: F: 22.3 ± 1.3 y/o M: 24.8 ± 1.0 y/o	mean ± SEM: F: 21.1 ± 0.6 kg/m^2, 25.9 ± 1.4% BF M: 23.7 ± 0.6 kg/m^2, 13.7 ± 1.4% BF	VO_{2peak} via treadmill GXT; mean ± SEM: F: 1.5 ± 0.1 L/min., M: 3.1 ± 0.1 L/min.
Chang SC & Wang JS, 2017[a] (16)	Aerobic, light-moderate intensity; 40 min. @ 60% VO_{2max} in hypoxia (12% O_2)	Healthy, Inactive	PBMCs; Pre- vs post-exercise	12, 100%, N/R	N/R	N/R
Ferrer MD et al., 2021[b] (23)	Aerobic, light-moderate intensity; 30 min. treadmill walk @ 60-70% HR_{max}	Overweight/obese men with MetS & BMI 27-40, capable of exercise	PBMCs; Pre- vs post-exercise (30 min.)	15, 100%, mean ± SEM: 66.5 ± 2.3 y/o	mean ± SEM: 29.3 ± 1.7 kg/m^2; WC: 102 ± 4 cm	N/R
Liepinsh E et al., 2020 (40)	Aerobic, light-moderate intensity; 60 min. exercise @ 50W	Healthy, Inactive	PBMCs; Pre- vs post-exercise	12, 42%, mean ± SEM: 36.2 ± 7.3 y/o	mean ± SEM: 25.1 ± 2.5 kg/m^2; N/R	Est. VO_{2max} via submaximal cycle ergometer GXT; mean ± SEM: 33.3 ± 1.3 ml/kg/min.
Bisset SK & Alexander WD, 1958 (7)	Aerobic, light-moderate intensity; 3-4 min. "moderate" treadmill exercise	Health and activity status N/R	PBMCs; Pre- vs post-exercise	6, N/R, 18-29 y/o	N/R	N/R

Notes: a= Data from conference abstract. b = data from placebo/control condition of study including dietary intervention. c = results relevant to this review taken from acute exercise session of larger study. d = T-cell nutrient transporter and metabolic enzyme expression analyzed from within PBMCs via Flow Cytometry. Abbreviations: %BF = body fat percentage; BMI = body mass index; BPM = beats per minute; F = female; GXT = graded exercise test; HR = heart rate; HR_{max}: maximum heart rate; M = male; MetS = metabolic syndrome; N/R = data relevant to review not reported; SD = standard deviation; SEM = standard error of the mean; VO_2 = volume of oxygen consumed per time unit; VO_{2max} = maximal volume of oxygen consumed per time unit; VO_{2peak} = peak volume of oxygen consumed per time unit; W_{max} = wattage at maximal aerobic exercise (VO_{2max}); WC = waist circumference; y/o = years old.

Author, year	Table 3: Report Characteristics - Effects of Exercise Training					
	Exercise Type and Intensity; Training	**Participants**	**Cell Population; Sampling Time Point**	**Participant Characteristics (N, % male, age)**	**Participant BMI, Body Composition**	**Fitness Assessment; Participant Fitness[d]**
Busquets-Cortes C et al., 2016[b] (12)	Aerobic, heavy-severe intensity; 8 weeks; 6 x 2 h soccer practice/week + 10 matches	Athletes (professional soccer players)	PBMCs; Pre- vs post- 8-week training	7, 100%, mean ± SEM: 18.9 ± 0.5 y/o	mean ± SEM: 23.1 ± 0.4 kg/m^2, mean ± SEM: 91.5 ± 0.3% FFM	N/R; mean ± SEM: 61.2 ± 1.6 ml/kg/min.
Gatterer H et al., 2018 (27)	Both groups: Aerobic, heavy-severe intensity; 3 weeks 3 days/week; cycle ergometer training in hypoxia RSH: 3 x 5 x10 s @ 85% BW w/ 20 s rest w/ 5 min. rest between series SIH: 4 x 30 s @ 0.75 x BW on 5 min. rest	Athletes (recreational)	PBMCs; Pre- vs post- 3-week training	All: 11, N/R, mean ± (error type not specified): 24.0 ± 2.4 y/o RSH: 6, N/R, 24.8 ± 2.5 y/o SIH: 5, N/R, 23.0 ± 2.1 y/o	N/R	*Wingate test:* RSH: mean ± (error type not specified): 811 ± 73 W, SIH: 789 ± 90 W *RS (5 x 6 s cycling sprints):* RSH: 1043 ± 89 W, SIH: 1000 ± 118 W *YYIR2:* RSH: 486.7 ± 134.9 m, SIH: 430.0 ± 50.3 m *RSA (6 x 34 m sprints w/ 20 s recovery):* RSH: 6.45 ± 0.36 s, SIH: 6.60 ± 0.26 s
Chang S & Wang J, 2015[a] (17)	Both groups: 6 weeks 5 days/week; 30 minutes cycling exercise: HIIT: Aerobic, heavy-severe intensity: alternating 3 min. @ 80% VO_{2max} & 40% VO_{2max} MICT: Aerobic, light-moderate intensity; continuous 60% VO_{2max}	Healthy, Inactive	Lymphocytes; Pre- vs post-training	HIIT: 12, 100%, N/R MICT: 12, 100%, N/R	N/R	N/R
Hasni S et al., 2021 (29)	Aerobic, heavy-severe intensity; 12 weeks 3 days/week; 30 min. treadmill exercise 70-80% $VO_{2reserve}$	SLE w/ fatigue, activity N/R	PBMCs; Pre- vs post-training	16, 0%, mean ± SD: 42.0 ± 10.3 y/o	N/R	Time to anaerobic threshold: N/R 10MWT; N/R
Hedges CP et al., 2019 (31)	Aerobic, heavy-severe intensity; 2 weeks, 6 training sessions; 8-12 x 60 seconds cycling @ W_{peak} interspersed with 75 seconds @ 30 watts	Healthy, Inactive	PBMCs; Pre- vs post-training	10, 100%, mean ± SEM: 24.7 ± 0.3 y/o	mean ± SEM: 24.1 ± 0.7 kg/m^2; N/R	VO_{2max} via cycle ergometer GXT; mean ± SEM: 3.3 ± 0.2 L/min.
Andonian B et al., 2020[a] (2)	Aerobic, heavy-severe intensity; 10 weeks high-intensity interval training	Rheumatoid arthritis, Inactive	T-cells; Pre- vs post-training	12 (n=6 PBMCs), N/R, N/R	N/R	N/R
Bartlett DB et al., 2020 (6)	Aerobic, heavy-severe intensity; 10 weeks 3 days/week; 20min. sessions alternating 60-90 seconds @ 80-90% $VO_{2reserve}$ vs. 60-90 seconds @ 50-60% $VO_{2reserve}$	Training group: Prediabetes, Inactive Control: Healthy, Active[c]	Neutrophils; Pre- vs post-training, vs control	Training group: 10, 40%, mean ± SD: 71 ± 5 y/o Control: 6, 50%, mean ± SD: 23 ± 1 y/o	Training group: mean ± SD: 29.4 ± 3.0 kg/m^2; 39.6 ± 8.6 % BF Control: mean ± SD: 25 ± 2.6 kg/m^2: N/R	Training group: VO_{2peak} via treadmill GXT; mean ± SD: 20 ± 2 ml/kg/min. 400 m walk test; 254 ± 27 s Berg balance scale; 54.3 ± 5.8 Grip strength; 27 ± 6.8 kg Timed-up and go; 8.9 ± 1.5 s

Morabito C et al., 2016 (49)	Aerobic, light-moderate intensity; 2 x12 days mountain trekking, ~6.5 h/day	Healthy, activity N/R	PBMCs; Pre- vs post-trekking at low altitude & high altitude	7, 0%, mean ± SEM: 36.3 ± 7.1 y/o	N/R	N/R
Brand S et al., 2020 (10)	Aerobic, light-moderate intensity; 12 weeks 3 days/week; supervised aerobic exercise @ 60-75% estimated HR_{max}	Training group: Self-reported occupational burnout, Inactive Control: Healthy, Inactive	Lymphocytes; Pre- vs post-training, vs control	Training group: 12, 100%, mean ± SD: 45.8 ± 6.8 y/o Control: 12, 100%, mean ± SD: 45.7 ± 5.7 y/o	N/R	N/R
Butcher LR et al., 2008 (14)	Aerobic, light-moderate intensity; 8 weeks 3 days/week; 10,000 steps on treadmill @ self-selected pace	Healthy, Inactive	PBMCs; Pre- vs post-training	All: 34, 53%, mean ± SD: 45.6 ± 11.1y/o Training: 17, N/R, mean ± SD: 44.94 ± 10.1 y/o Control: 17, N/R, mean ± SD: 46.12 ± 12.2 y/o	Training: mean ± SD: 26.78 ± 5.11 kg/m^2, 33.78 ± 10.25% BF Control: mean ± SD: 27.02 ± 5.32 kg/m^2, 34.15 ± 10.03% BF	Estimated VO_{2max} via Rockport submaximal treadmill test; Training: mean ± SD: 35.49 ± 6.49 ml/kg/min. Control: mean ± SD: 34.62 ± 5.68 ml/kg/min.
Kocher M et al., 2017 (36)	Aerobic, light-moderate intensity; 12 weeks; 20 min./session @ 50-80% HR_{max} increased 2 min./week to 40 min./session	HIV^+, Inactive	PBMCs; Pre- vs post- training	7, 100%, 36-58 y/o	Median ± (error type not specified): 24.6 ± 4.2 kg/m^2	VO_{2peak} via cycle ergometer GXT; N/R
Yakeu G et al., 2010 (73)	Aerobic, light-moderate intensity; 8 weeks 3 days/week; 10,000 steps on treadmill at self-selected pace	Healthy, Inactive	PBMCs; Pre- vs mid- vs post-training	17, 53%, mean ± SD: 45.6 ± 11.1 y/o	mean ± SD: 26.78 ± 5.11 kg/m^2	N/R
Lehti M et al., 2020 (38)	Concurrent Exercise; 21 weeks 2 days/week; MIAST @ 50-60% $HR_{reserve}$ (later increased to 85%) for 1h	Coronary artery disease, Inactive	PBMCs; Pre- vs post-training, training vs control	Training: 12, 92%, mean ± SD: 58.6 ± 8.5 y/o Control: 11, 82%, mean ± SD: 63.3 ± 6.1 y/o	Training: mean ± SD: 27.1 ± 3.0 kg/m^2 Control: mean ± SD: 27.9 ± 4.2 kg/m^2	VO_{2peak} via cycle ergometer; Training: mean ± SD: 25.8 ± 5.3 ml/kg/min. Control: mean ± SD: 23.2 ± 4.9 ml/kg/min.
Estebanez B et al., 2019 (21)	Resistance Exercise; 8 weeks 2 days/week; full body RT 3 x 12/8/12 repetitions of 8 exercises	Heathy, Active (resistance training naïve)	PBMCs; RT experiment: Pre- vs post- 8-week RT (old), Aging: baseline old vs young	RT experiment: All: 30, 37%, mean ± SEM: 72.8 ± 2.2 y/o Training: 20, N/R, mean ± SEM: 73.7 ± 2.2 y/o Control: 10, N/R, mean ± SEM: 73.8 ± 2.3 y/o Young: 10, N/R, mean ± SEM: 22.5 ± 2.3 y/o	RT experiment: Training: mean ± SEM: 27.5 ± 0.7 kg/m^2 Control: mean ± SEM: 28.5 ± 0.8 kg/m^2 Young: mean ± SEM: 24.6 ± 2.5 kg/m^2	MVIC for leg press & bicep curl; Training: mean ± SEM: 76.0 ± 5 kg, 48.5 ± 4.3 kg Control: N/R 1RM for leg press, bicep curl, pec deck; Training: mean ± SEM: 71.0 ± 4.7 kg, N/R, 55.0 ± 6.9 kg Control: N/R

Notes: a = Data from conference abstract; b = data from placebo/control condition of study including dietary intervention, or in which all participants received same dietary treatment; c = healthy highly active participants only used for baseline comparisons; d = baseline fitness data. Abbreviations: 1RM = 1-repetition maximum; 10MWT = 10-meter walk test; %BF = body fat percentage; BMI = body mass index; BW = body weight; %FFM = fat-free mass percentage; GXT = graded exercise test; HIIT = high-intensity interval training; HR_{max} = maximal heart rate; $HR_{reserve}$ = heart rate reserve, HR_{max} - HR_{rest}; MICT = moderate-intensity continuous training; MIAST = mixed interval-type aerobic and strength training; MVIC = maximal voluntary isometric contraction; N/R = data relevant to review not reported; PBMC = peripheral blood mononuclear cell; RSA = repeated sprint ability (running); RSH = repeated-sprint training in hypoxia; RT = resistance training; RS = repeated cycling sprints; SD = standard deviation; SEM = standard error of the mean; SIH = sprint-interval training in hypoxia; SLE = systemic lupus erythematosus; VO_{2max} = maximal volume of oxygen consumed per time unit; VO_{2peak} = peak volume of oxygen consumed per time unit; $VO_{2reserve}$ = reserve VO_2, VO_{2max} -VO_{2rest}; W_{peak} = peak wattage during exercise test; y/o = years old; YYIR2 = yo-yo intermittent recovery test level 2

Author, year	Table 4: Report Characteristics - Effects of Physical Fitness				
	Participants	**Cell Population; Comparator(s)**	**Participant Characteristics (N, % male, age)**	**Participant BMI, Body Composition**	**Fitness Assessment; Participant Fitness**
Alley JR, Valentine RJ, Kohut ML, 2022 (1)	Healthy, Inactive and Active	RBC-lysed blood, PBMCs; PA level/ CRF	Inactive: 15, 53%, mean ± SD: 24 ± 6 y/o Active: 15, 47%, mean ± SD: 23 ± 3 y/o	Inactive: mean ± SD: 21.7 ± 1.5 kg/m^2, 23.6 ± 5.3% BF Active: mean ± SD: 21.6 ± 1.5 kg/m^2, 15.6 ± 4.0% BF	VO_{2peak} via treadmill GXT; Inactive: mean ± SD: 42.7 ± 7.4 ml/kg/min. Active: mean ± SD: 59.6 ± 9.0 ml/kg/min.
Antunes BM et al., 2020[a] (3)	Healthy, Inactive and Active	Monocytes; CRF	22, 100%, mean ± (error type not specified):25.8 ± 5.7 y/o	N/R	VO_{2max} (ml/kg/min.) via cycle ergometer GXT; Low-fit: mean: 35.3 ml/kg/min. High-fit: mean: 63.1 ml/kg/min.
Dorneles GP et al., 2021[a] (20)	Healthy, Inactive and Active	PBMCs; CRF	22, 100%, mean ± SD: 26.8 ± 3.1 y/o	Low-fit: mean ± SD: 23.9 ± 1.2 kg/m^2, 81.2 ± 7.8 cm WC Moderately-fit: mean ± SD: 23.5 ± 1.1 kg/m^2, 80.7 ± 4.1cm WC High-fit: mean ± SD: 23.8 ± 1.6 kg/m^2, 78.1 ± 6.3 cm WC	VO_{2peak} via treadmill GXT; Low-fit: mean ± SD: 38.1 ± 1.7 ml/kg/min. Moderately-fit: mean ± SD: 43.9 ± 2.7 ml/kg/min. High-fit: mean ± SD: 55.1 ± 4.7 ml/kg/min.
Mota MP et al., 2010 (50)	Healthy, Inactive and Active	Lymphocytes; CRF, age	Low fit young (LFY): 8, 100%, mean ± SD: 20.8 ± 1.0 y/o High fit young (HFY): 13, 100%, mean ± SD: 23.0 ± 3.7 y/o Low fit adult (LFA): 9, 100%, mean ± SD: 37.0 ± 3.6 y/o High fit adult (HFA): 9, 100%, mean ± SD: 32.8 ± 3.4 y/o Low fit middle aged (LFM): 13, 100%, mean ± SD: 48.9 ± 5.4 y/o High fit middle aged (HFM): 14, 100%, mean ± SD: 46.1 ± 3.5 y/o	N/R	VO_{2max} via treadmill GXT; (all mean ± SD): LFY: 42.9 ± 5.1 ml/kg/min. HFY: 57.4 ± 3.9 ml/kg/min. LFA: 38.5 ± 1.9 ml/kg/min. HFA: 51.3 ± 3.3 ml/kg/min. LFM: 33.9 ± 5.5 ml/kg/min. HFM: 49.1 ± 5.5 ml/kg/min.
Vladutiu GD et al., 2002 (69)	4 sisters w/ genetic CPT2 deficiency; Healthy Inactive; Healthy Athlete	Leukocytes in whole blood; Health status, training status	Sisters: 4, 0%, 24-30 Inactive: 20, 0%, mean ± (error type not specified): 24 ± 3 y/o Athlete: 24, 0%, mean ± (error type not specified): 33 ± 2 y/o	N/R	VO_{2max} via treadmill GXT; Sisters: range: 36.5-43.6 ml/kg/min. Inactive: 34.3 ml/kg/min. (central tendency not specified) Athlete: 47.9 ml/kg/min. (central tendency not specified)
Farinha JB et al., 2015 (22)	Overweight or obese, Inactive and Active	PBMCs; PA level	All: 35, 0%, N/R (Postmenopausal) Inactive: 12, 0%, mean ± SD: 56.25 ± 4.76 y/o Active: 23, 0%, mean ± SD: 53.82 ± 5.49 y/o	All: BMI >25 kg/m^2 Inactive: mean ± SD: 32.99 ± 4.38 kg/m^2, 97.58 ± 11.13 cm WC Active: mean ± SD: 31.07 ± 5.12 kg/m^2, 90.29 ± 10.68 cm WC	VO_{2max} via treadmill GXT; Inactive: mean ± SD: 18.6 ± 2.01 ml/kg/min. Active: mean ± SD: 22.22 ± 4.67 ml/kg/min.
Tyrrell DJ et al., 2015 (67)	Overweight or obese, Inactive	PBMCs; Physical fitness	15, 60%, mean ± SD: 68.3 ± 3.5 y/o	mean ± SD: 30.8 ± 2.4 kg/m^2; 8.3 ± 1.6 kg leg lean mass	Ex-SPPB; mean ± SD: 2.5 ± 0.3 400 m walk test; mean ± SD: 1.5 ± 0.5 m/s Grip strength; mean ± SD: 35.6 ± 10.7 kg Knee extension; mean ± SD: 122.0 ± 36.0 Nm

a=results relevant to this review taken from a single phase of larger study. Abbreviations: %BF = body fat percentage; BMI = body mass index; CPT2 = carnitine palmitoyltransferase 2; CRF=cardiorespiratory fitness; Ex-SPPB = expanded short physical performance battery score; GXT= graded exercise test; HFA = high-fit adult group; HFM = high-fit middle-aged adult group; HFY = high-fit young adult group; LFA = low-fit adult group; LFM = low-fit middle-aged adult group; LFY = low-fit young adult group; N/R = data relevant to review not reported; PA = physical activity; RBC= red blood cell; SD = standard deviation; VO_2 = volume of oxygen consumed per time unit; VO_{2max} = peak volume of oxygen consumed per time unit; VO_{2peak} = peak volume of oxygen consumed per time unit; WC = waist circumference; y/o = years old.

Author, year	Table 5: Report Characteristics - Effects of Acute Exercise plus Physical Fitness or Exercise Training						
	Exercise Type and Intensity; Session	**Exercise Type and Intensity; Training**	**Participants**	**Cell Population; Sampling Time Points; Comparators**	**Participant Characteristics (N, % male, age)**	**Participant BMI, Body Composition**	**Fitness Assessmenta nd Participant Fitness[a]**
Janssen JJE et al., 2022 (34)	Aerobic, heavy-severe intensity; 60 min. cycle ergometer @ 70% VO_{2peak}	N/A	Healthy, Low-fit & High-fit	PBMCs; CRF, Pre- vs post-exercise (21h)	Low-fit: 16, 0%, median [IQR]: 24.0 y/o [21.3-25.5] High-fit: 15, 0%, median [IQR]: 21.8 y/o [21.6-23.7]	Low-fit: N/R, mean ± SD: 28.9 ± 3.9% BF High-fit: N/R, mean ± SD: 25.1 ± 4.4% BF	VO_{2max} via cycle ergometer GXT; Low-fit: median [IQR]: 35.1 ml/kg/min. [32.2-35.7] High-fit: median [IQR]: 50.4 ml/kg/min. [49.0-54.0]
Pendergast DR et al., 2004 (53)	Aerobic, heavy-severe intensity; GXT to exhaustion via treadmill	N/A	Four groups: Afflicted with disease; Healthy, inactive; Healthy, athletes (elite runners, recreational runners)	Leukocytes in whole blood; Health/ training status, pre- vs post-exercise	Inactive: 43, N/R, 20-40 y/o Inactive + Acute Exercise: 12, 42%, 20-30 y/o Active: 12, 50%, 27-45 y/o Athletes: 5, 100%, 26-32 y/o CPT2 def: 2, 0%, 24 & 29 y/o MS: 31, 16%, 30-45 y/o CFS: 6, 0%, 30-45 y/o OB: 5, 40%, 18-35 y/o ED: 16, 0%, 16-25 y/o	N/R	N/R
Busquets-Cortes C et al., 2017 (13)	Aerobic, heavy-severe intensity; Leger-Boucher test pre- and post-training + sport drills post-training	Aerobic, heavy-severe intensity; 8 weeks, 5 x 2 h soccer practice + 1 game/week	Athletes (professional soccer players)	PBMCs; Pre- vs post-training, pre- vs post-exercise (2 h)	12, 100%, mean ± SEM: 19.3 ± 0.4 y/o	mean ± SEM: 24.0 ± 0.6 kg/m^2, mean ± SEM: 92.5 ± 0.2% FFM	Estimated VO_{2max} via Leger-Boucher test; mean ± SEM: 60.4 ± 1.8 ml/kg/min.
Thomas AW et al., 2012 (65)	Aerobic, heavy-severe intensity; 45 min. cycle ergometer @ 70% VO_{2max}	Aerobic, heavy-severe intensity; 8 weeks 2-4 sessions/weekc ycle ergometer @ 60-85% VO_{2max} for 30-60 min.	Healthy, Active	PBMCs; Pre- vs post-training, pre- vs post-exercise	Acute exercise: 9, N/R, mean ± SEM: 32 ± 8 y/o Training: 8, N/R, mean ± SEM:27.8 ± 6.4 y/o	N/R	VO_{2max} via cycle ergometer GXT pre - & post-training; N/R

Lin ML et al., 2022 (41)	Aerobic, heavy-severe intensity; same as exercise test (GXT)	Both: 6 weeks 5 days/week cycle training: HIIT: Aerobic, heavy-severe intensity: 5 x 3 min. @ 80% VO_{2max} then 3 min. @ 40% VO_{2max}; or MICT: Aerobic light-moderate intensity: 30 min. @ 60% VO_{2max}	Healthy, Inactive	NK cells; Pre- vs post-training, training protocol	HIIT: 20, 100%, mean ± SEM: 22.2 ± 2.1 y/o MICT: 20, 100%, mean ± SEM: 22.3 ± 2.8 y/o Control: 20, 100%, mean ± SEM: 22.6 ± 2.7 y/o	mean ± SEM: HIIT: 24.3 ± 3.1 kg/m^2, N/R MICT: 23.3 ± 2.9 kg/m^2, N/R Control: 24.0 ± 2.8 kg/m^2, N/R	VO_{2max} via cycle ergometer GXT pre- & post-training; mean ± SEM: HIIT: 33.5 ± 4.8 ml/kg/min. MICT: 33.2 ± 4.5 ml/kg/min. Control: 32.2 ± 4.1 ml/kg/min.
Tsai HH et al., 2016 (66)	Aerobic, light-moderate intensity; 36 min. cycling @ 50-100w in hypoxia (12% O_2)	Both: 6 weeks 5 days/week cycle training: HIIT: Aerobic, heavy-severe intensity: 5 x 3 min. @ 80% VO_{2max} then 3 min. @ 40% VO_{2max} MICT: Aerobic light-moderate intensity 30min. @ 60% VO_{2max}	Healthy, Inactive	Lymphocytes; Pre- vs post-training, pre- vs post-hypoxic exercise, training protocol	HIIT: 20, 100%, mean ± SEM: 22.2 ± 2.1 y/o MICT: 20, 100%, mean ± SEM: 22.3 ± 2.8 y/o Control: 20, 100%, mean ± SEM: 22.6 ± 2.7 y/o	mean ± SEM: HIIT: 22.5 ± 0.6 kg/m^2; N/R MICT: 22.6 ± 0.7 kg/m^2; N/R Control: 22.7 ± 0.6 kg/m^2; N/R	VO_{2max} via cycle ergometer GXT pre- & post-training; mean ± SEM: HIIT: 34.0 ± 1.4 ml/kg/min. MICT: 33.1 ± 1.2 ml/kg/min. Control: 32.2 ± 1.0 ml/kg/min.

Notes: a= baseline fitness data. Abbreviations: %BF = body fat percentage; BMI = body mass index; CFS = individuals with chronic fatigue syndrome; CPT2 def.= individuals with carnitine palmitoyltransferase 2 deficiency; CRF = cardiorespiratory fitness; ED = individuals with eating disorder, anorexia nervosa; %FFM = fat-free mass percentage; GXT = graded exercise test; HIIT = high-intensity interval training; IQR = interquartile range; MICT = moderate intensity continuous training; MS = individuals with multiple sclerosis; N/A = not applicable; N/R = not reported; OB = individuals with obesity; SD = standard deviation; SEM = standard error of the mean; VO_{2max} = maximal volume of oxygen consumed per time unit; VO_{2peak} = peak volume of oxygen consumed per time unit; y/o = years old.

Author, Year	Table 6: Key Findings - Reports Evaluating Effects of Acute Exercise			
	Cell Number and Phenotype	**Metabolic Regulation**	**Metabolic Function**	**Cell Function**
Heavy-Severe Intensity AE				
Busquets-Cortes C et al., 2017[c] (13)	No difference in # PBMC's or % lymphocytes, % monocytes (2 h post-exercise)	↑PBMC COXIV, PGC-1α, MitND5 mRNA expression (2 h post-exercise) ↑PBMC UCP2, PGC-1α, Mfn-2 protein expression (2 h post-exercise)	N/R	↑PBMC intracellular ROS and H_2O_2 production in PMA-stimulated PBMCs (2 h post-exercise) ↑NF-κB activation, (2 h post-exercise)
Capo X et al., 2020[b,c] (15)	N/R	↑PBMC SIRT3 mRNA expression (2 h post-exercise)	N/R	N/R
Ferry A, Marsac C, Duvallet A, Rieu M, 1991 (24)	N/R	N/R	Mean ± SD: ↓33.6 ± 6.6% lymphocyte PDHc activity ↑43.1 ± 4.7% lymphocyte CS activity No change lymphocyte COX or SCR activity per mg protein	N/R
Hunter DJ et al., 2019[b] (33)	N/R	↓ PBMC PGC-1α gene methylation ↑PBMC PGC-1α mRNA expression +Correlation PBMC PGC-1α gene methylation vs. TT cycling mean power ($\rho = 0.714$, $p < 0.05$) -Correlation PBMC PGC-1α gene methylation vs. PBMC protein carbonyls ($\rho = -0.714$, $p < 0.05$)	N/R	N/R
Nieman DC et al., 2018[b] (Water-only vs. CHO-conditions) (51)	#Leukocytes > CHO-conditions immediately, 0.75 h, 1.5 h, 3 h, 4.5 h post-exercise	N/R	↓THP-1 average OCR following water-only plasma incubation (6 h) vs. CHO-conditions (immediately post-exercise plasma) THP-1 SRC following water-only plasma incubation (37.9%) < CHO-conditions (avg. 95.8%) (immediately post-exercise plasma) ↑THP-1 average ECAR following water-only plasma incubation (6 h) vs. CHO-conditions (immediately post-exercise plasma)	No change THP-1 COX-2 expression following culture (6 h) with immediately post-, 1.5h post-, or 21h post-exercise plasma vs. pre-exercise Greater THP-1 COX-2 expression with water-only 21 h plasma vs. CHO food conditions.
Janssen JJE et al., 2022[c] (34)	↓# PBMCs (21 h post-exercise) ↓% $CD4^+CD25^+$ T cells and $CD4^+CD25^+$ $CD127^+$ T cells (low-fit only) (21 h post-exercise)	N/R	No change in PBMC OCR or PER (21 h post-exercise)	N/R
Pendergast DR et al., 2004[c] (53)	↑#leukocytes in sedentary & elite runners	N/R	↑Total leukocytes FA oxidation in sedentary No difference leukocytes FA oxidation per cell in sedentary No change total leukocytes FA oxidation in elite runners ↓leukocytes FA oxidation per cell in elite runners	N/R
Davies NA et al., 2015[b] (18)	N/R	↑PBMC PGC-1α, PPARγ, ABCA1 mRNA expression (3 h post-exercise) No change PBMC AMPK protein phosphorylation (3 h post-exercise)	N/R	N/R

Frisina JP et al., 1994 (26)	↓$CD3^+$ & $CD20^+$ cells, $CD4^+$:$CD8^+$ ratio (3 min. post-exercise) ↑$CD56^+$ cells (3 min. post-exercise)	N/R	↑18.69% lymphocyte glutamine oxidation (3 min. post-exercise) ↑27.02% lymphocyte lactate production (3 min. post-exercise) +Correlation glutamine oxidation vs. %change NK cells ($r = 0.78$, $p < 0.01$) -Correlation glutamine oxidation vs. %change T cells ($r = -0.93$, $p < 0.001$) -Correlation lactate production vs. %change T cells ($r = -0.66$, $p < 0.01$)	↓58% lymphocyte Con-A (3.5 μg/mL, 48hrs) stimulated proliferation (3 min. post-exercise) +Correlation %change proliferation vs. %change T cells ($r = 0.78$, $p < 0.01$) -Correlation %change proliferation vs. %change NK cells ($r = -0.76$, $p < 0.05$)
Moir H et al., 2010 (48)	↑#leukocytes 0 h, 1 h	↓PBMC PGC-1α mRNA expression (0 h post-exercise) No change PBMC PGC-1α mRNA expression (1 h post-exercise) ↓PBMC AMPK protein phosphorylation (0 h post-exercise) No change PBMC AMPK protein phosphorylation (1 h post-exercise)	N/R	↓PBMC Unstimulated and PMA-stimulated (25 ng/mL, 10 min) ROS (0 h post-exercise)
Moir et al., 2008 (47)	↑#leukocytes 0 h, 1 h	No change Monocyte CD36 mRNA expression (0 h, 1 h post-exercise) ↓Monocyte AMPK protein phosphorylation (0 h post-exercise) No change Monocyte AMPK protein phosphorylation (1 h post-exercise) No change intracellular ATP	N/R	N/R
Thomas AW et al., 2012[c] (65)	N/R	↑PBMC CD36 & ABCA1 mRNA expression (3 h post-exercise)	N/R	N/R
Theall B et al., 2022 (64)	↑%, #naïve ($KLRG^-$/$CD57^-$) and senescent ($KLRG^+$/$CD57^+$) $CD8^+$ T cells ↑#very-early ($CD69^+$), early ($CD25^+$), and late ($CD71^+$) activated $CD8^+$ T cells ↑#early ($CD25^+$) and late ($CD71^+$) activated $CD4^+$ T cells ↑% but not # $CD38^+$ (late activation) $CD4^+$ and $CD8^+$ T cells	↑#$GLUT4^+$ $CD4^+$ T cells ↓%$CD36^+$ CD8, % $HK2^+$ $CD4^+$, % and # $HK1^+$ $CD4^+$, % $HK1^+$ $CD8^+$ T cells +Correlation # $CD69^+$ and $CD25^+$ $CD8^+$ T cells vs. # $GLUT1^+$ $CD8^+$ T cells ($\rho = 0.672$, p 0.001 & $\rho = 0.391$, $p = 0.088$) +Correlation $CD69^+$ and $CD38^+$ $CD4^+$ T cells vs. $GLUT1^+$ $CD4^+$ T cells ($\rho = 0.528$ & $\rho = 0.577$) +Correlation # $CD38^+$ $CD4^+$ T cells vs. $HK1^+$ $CD4^+$ T cells ($\rho = 0.556$, $p = 0.039$) +Correlation $CD71^+$ and $CD38^+$ $CD4^+$ T cells vs. $CD36^+$ $CD4^+$ T cells ($\rho = 0.635$, $p = 0.003$ & $\rho = 0.630$, $p = 0.003$)	No change PBMC routine, leak, OXPHOS, ETS & RCRs per 10^6 cells ↑Routine ($d = 0.58$), routine (PMG) ($d = 0.77$), Leak (PMGS) ($d = 0.80$), OXPHOS ($d = 0.80$), ETS ($d = 0.78$) respiration per mL blood	N/R
Meksawan K et al., 2005[b] (44)	↑#leukocytes	N/R	↓leukocyte FA oxidation per cell ↑leukocyte FA oxidation per mL blood	N/R
Lin ML et al., 2022[c] (41)	↑#NK cell ↑#$CD45RA^+$ & $CD57^+$ NK cell ↓#$CD45RO^+$ NK cell	No change NK cell mitochondrial content or MMP ↑NK cell MOB	↑NK cell ETS & Reserve OCR & BHI	↑NK cell Perforin & Granzyme B

Light-Moderate Intensity AE				
Chang SC & Wang JS, 2017[a] (16)	N/R	↑PBMC MMP	No change PBMC routine or maximal OXPHOS respiration ↓PBMC CI respiration	N/R
Ferrer MD et al., 2021[b] (23)	N/R	↓PBMC COXIV & Tfam mRNA expression (30 min. post-exercise) No change PBMC UCP3, MnSOD, COXIV, Mtf1, Mtf2 protein expression (30 min. post-exercise)	N/R	N/R
Liepinsh E et al., 2020[b] (40)	N/R	N/R	↑31% PBMC routine respiration (15 min. post-exercise) ↑65% PBMC FA-dependent leak respiration (15 min. post-exercise) ↑76% PBMC FA-dependent OXPHOS (15 min. post-exercise) ↑22% PBMC FA coupling efficiency (15 min. post-exercise)	N/R
Tsai HH et al., 2016[c] (66)	↑#Lymphocyte & %$CD57^+$ lymphocytes ↓% $CD62L^+$ & $CD28^+$ lymphocytes	No change mitochondrial biogenesis or metabolic regulatory proteins No change in mitofusin or Drp-1 No change lymphocyte mitochondrial count ↓lymphocyte MMP, ↑MOB	↓Lymphocyte ATP-linked OCR, reserve OCR, OCR via CI and CII substrates ↑Lymphocyte LDH & GDH activity ↓ Lymphocyte CS activity	N/R
Bisset SK & Alexander WD, 1958 (7)	No change #leukocytes (5 min. post-exercise)	N/R	↑36-71% leukocyte VO_2 (5 min. post-exercise)	N/R

Notes: Data derived from blood samples obtained immediately post-exercise unless otherwise noted. a = Data from conference abstract. b = Data from placebo/control condition of study including dietary intervention, or in which all participants received same treatment. c = acute exercise data from larger study. Abbreviations: ABCA1 = ATP binding cassette subfamily A member 1; AMPK = AMP-activated protein kinase; ATP = adenosine triphosphate; BHI = bioenergetic health index; CHO = carbohydrate; CI = complex 1 of mitochondrial electron transport chain; CII = complex II of mitochondrial electron transport chain; Con-A = concanavalin A; COX = cytochrome c oxidase; COXIV = cytochrome C oxidase subunit 4; CS = citrate synthase; Drp-1 = dynamin-related protein 1; ETS = electron transport system; FA = fatty acid; GDH = glutamate dehydrogenase; LDH = lactate dehydrogenase; Mfn-2 = mitofusin-2; MitND5 = mitochondrial NADH dehydrogenase subunit 5; MMP = mitochondrial membrane potential; MOB = mitochondrial oxidant burden; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; N/R = data relevant to review not reported; OCR = oxygen consumption rate; OXPHOS = oxidative phosphorylation; PBMC = peripheral blood mononuclear cells; PER = proton efflux rate; PDHc = pyruvate dehydrogenase complex; PGC-1α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ = peroxisome proliferator-activated receptor gamma; RCR = respiratory control ratio; ROS = reactive oxygen species; SCR = succinate cytochrome reductase; SD = standard deviation; SIRT3 = NAD-dependent deacetylase sirtuin-3, mitochondrial; SRC = spare respiratory capacity; Tfam = transcription factor A, mitochondrial; THP-1 = human monocytic cell line; TT = time trial; UCP2 = uncoupling protein 2; VO_2 = volume of oxygen consumed per time.

Author, Year	Table 7: Key Findings-Reports Evaluating Effects of Exercise Training				
	Training Response	**Cell Number, Proportion, and Phenotype**	**Metabolic Regulation**	**Metabolic Function**	**Cell Function**
Heavy-Severe Intensity AE training					
Busquets-Cortes C et al., 2016[b] (12)	N/R	No change # PBMCs, % lymphocytes, % monocytes	↑PBMC Tfam, OPA1, OMA1 protein expression	N/R	No change PMA-stimulated (10 ng/mL) PBMC H_2O_2 production ↓PBMC MDA ↑PBMC protein carbonyls
Busquets-Cortes C et al., 2017[g] (13)	No change estimated VO_{2max} pre vs. post 8 wks training	No change in # PBMC's or % lymphocytes, % monocytes	No change PBMC COXIV, PGC-1α, MitND5 gene expression ↑PBMC UCP2, UCP3, COXIV, Mfn-1, and ↓PBMC Tfam protein expression	N/R	No change PBMC NF-κB activation, PMA-stimulated (10 ng/mL) H_2O_2 production
Gatterer H et al., 2018 (27)	↑YYIR2 running distance, RSA performance (RSH & SIH) ↑Wingate & RS mean and peak power (RSH & SIH) ↑RS skeletal muscle deoxygenation and re-oxygenation(RSH)	N/R	N/R	↓PBMC ETS per cell (RSH, n=2) ↓ETS normalized to CS activity (RSH & SIH, n=2/group)	N/R
Thomas AW et al., 2012[g] (65)	↓HR, blood lactate during submaximal exercise test No change VO_{2max}	N/R	↑PBMC CD36 protein expression No change PBMC PPARγ, phosphor-PPARγ:non-phospho-PPARγ protein expression	N/R	N/R
Hasni S et al. 2021[a] (29)	↑Time to anaerobic threshold, 10MWT performance	N/R	N/R	↑PBMC OCR/ECAR -Correlation FSS scores vs. OCR/ECAR	N/R
Hedges CP et al., 2018 (31)	↑VO_{2peak} (L/min)	No change #leukocytes, lymphocytes, #monocytes	No change PBMC PGC-1α, Tfam, NRF1, NRF2, COXIV gene expression No change PBMC mitochondrial CI-CV protein expression	No change PBMC mitochondrial respiration No correlation ΔPBMC mitochondrial respiration vs. Δskeletal muscle mitochondrial respiration	N/R
Andonian B et al., 2020[a] (2)	N/R	N/R	N/R	+Correlation ΔCRF vs. $\Delta CD4^+$ T cell basal and maximal respiration (ρ = 0.89, both) +Correlation $\Delta CD4^+$ T cell mitochondrial respiration vs. $\Delta CD4^+CCR7^+CD45RA^+$ T cells (ρ = 0.89)	N/R
Bartlett et al., 2020 (6)	Training group: ↑16 ± 11% VO_{2peak} ↓400m walk time	Training group: ↓#leukocytes (p = 0.059) No change # neutrophils	Training group: ↑Neutrophil MMP (d = 1.10)	Training group: ↑Neutrophil basal respiration (d = 3.01), maximal respiration (d = 2.86), ATP production (d = 4.18) ↓Neutrophil proton leak (n = 5) (d = 2.02)	Training group: ↑Neutrophil E. coli phagocytosis (d = 0.85), PMA-stimulated (25nM) ROS (d = 0.98), chemotaxis (d = 0.97), chemotactic index (d = 1.12)

					↓Neutrophil basal ROS (d = 0.93) +Correlation %ΔVO_{2peak} vs. neutrophil chemotaxis (r = 0.649, p = 0.042) -Correlation Δbody fat vs. neutrophil chemotaxis (r = -0.721, p = 0.018)
Heavy-Severe Intensity AE and Light-Moderate Intensity AE training Groups					
Chang SC & Wang JS, 2015[a] (17)	N/R	N/R	N/R	↑Lymphocyte ATP-linked OCR & ↓non-mitochondrial OCR (HIIT & MICT) ↑Lymphocyte pyruvate + glutamate-mediated OCR (HIIT only) ↑Lymphocyte succinate- & palmitoyl carnitine-mediated OCR (MICT only)	N/R
Lin ML et al., 2022[g] (41)	↑Vt, $Watts_{max}$, VE_{max}, VO_{2max}, VCO_{2max} (HIIT & MICT) HIIT Δ$Watts_{max}$, ΔVE_{max} > MICT	HIIT & MICT: ↑Resting & post-exercise #total & CD56dim NK cells ↓Resting & post-exercise %$CD45RA^+$ & $CD57^+$ NK cells ↑Resting & Post-Exercise #$CD45RO^+$ NK cells	HIIT & MICT: ↑Mitochondrial content & MMP @ rest & post-exercise ↓MOB post-exercise	↑NK cell ETS, Reserve OCR, BHI @ rest (HIIT & MICT) +Correlation ΔVO_{2max} vs. ΔNK cell ETS (r = 0.549) & Reserve OCR (r = 0.655) & BHI (r = 0.546)	↑NK cell perforin and granzyme b @ rest (HIIT & MICT)
Tsai HH et al., 2016[g] (66)	↑Watts, HR, VE, VO_2, VCO_2 @ V_t, exercise time to V_t (HIIT & MICT) ↑$Watts_{max}$, VE_{max}, $VO_{2max,}$ VCO_{2max}, time to max (HIIT & MICT) HIIT ΔCardio-pulmonary measures, Δtime to V_t, Δtime to max > MICT	HIIT & MICT: ↓HE-induced rise in total lymphocytes ↑% $CD28^+$, ↓%$CD57^+$ lymphocytes @ rest No change%$CD11a^+$, $CD45RA^+$, or $CD54RO^+$ cells @ rest or post-HE HIIT only: ↑%$CD28^+$,↓%$CD57^+$ lymphocytes post-HE	HIIT & MICT: No change mitochondrial biogenesis proteins ↓mitofusin & Drp-1 ↓HE-induced change MMP ↓HE-induced MOB HIIT only: ↑mitofusin: Drp-1 @ rest and immediately post-exercise ↑MMP @ rest & post-HE	HIIT & MICT: ↑ATP-linked OCR and Reserve OCR @ rest and post-HE ↑CII-linked OCR and OXPHOS capacity @ rest, ↓HE-induced respiratory changes ↓HE-induced changes in LDH & CS activity ↑SDH activity @ rest & post-HE	N/R
Light-Moderate Intensity AE training					
Morabito C et al., 2016 (49)	N/R	low-ALT: No change # PBMCs ↑% $CD69^+$ $CD4^+$ and $CD8^+$ T cells high-ALT: ↑% B cells, % $CD25^-CD69^-$ B cells, ↓% T cells, ↑% $CD69^+$ $CD8^+$ T cells	low-, high-ALT: No change PBMC HIF-1α protein expression No change MMP high-ALT: ↓mtROS among total & $CD3^+$	high-ALT: ↑PBMC metabolic activity via MTT staining	low-, high-ALT: No change intracellular ROS or NO
Brand S et al., 2020 (10)	N/R	N/R	N/R	Training group: ↑Lymphocyte mitochondrial OXPHOS (d = 1.27) & ETS (d = 1.67) respiration, Complex IV activity (d = 1.08) at Post-training Training group: Lymphocyte ATP content < Control at Baseline (d = 1.4),	N/R

				increased pre- to post-training (d = 0.91) -Correlation Lymphocyte ATP content vs. burnout score across sample (r = -0.62, p < 0.001)	
Butcher LR et al., 2008 (14)	Training: No change VO_{2max} (mean ± SD: +2.74 ± 4.21 ml/kg/min) Control: No change VO_{2max} (mean ± SD: +1.53 ± 2.63 ml/kg/min)	N/R	Training: PBMC CD36 & PPARγ gene expression @ 4 wks, 8 wks > Control or Baseline Training: PBMC ABCA1, ABCG1 gene expression @ 8 wks > Control or Baseline	N/R	N/R
Kocher M et al., 2017 (36)	↑14% VO_{2max}	No change in #$CD4^+$ T cells, viral load	N/R	↑PBMC non-mitochondrial respiration, respiratory capacity, SRC	N/R
Yakeu G et al., 2010 (73)	N/R	N/R	↑PBMC PGC-1α, PPARα gene expression @ 4 & 8 wks ↑PBMC PGC-1β gene expression @ 8 wks	N/R	N/R
Other Exercise Training					
Lehti M et al., 2020 (38)	Training group ↑VO_{2peak} at 12 weeks, trend (p = 0.06) for VO_{2peak} time x group effect (training vs. control) Training group ↑knee extensor MVIC 0 vs. 21 & 12 vs. 21 wks, time x group effect (p = 0.02)	N/R	Training group: ↑PBMC OXPHOS gene expression (z=3.27) (n=7)	N/R	N/R
Estebanez B et al., 2019 (21)	Training group ↑leg press, bicep curl MVIC + 1RM	N/R	Training group ↑PBMC PGC-1α, Mfn1 protein expression	N/R	N/R

Notes: a = Data from conference abstract; b = data from placebo/control condition of study including dietary intervention, or in which all participants received same dietary treatment; g = training results of a larger study. Abbreviations: 10MWT = 10-meter walk test; 1RM = 1-repitition maximum; ABCA1 = ATP binding cassette subfamily A member 1; ABCG1 = ATP binding cassette subfamily G member 1; ATP = adenosine triphosphate; BHI = bioenergetic health index; CI-CV = complexes 1-5 of the mitochondrial electron transport chain; CII = complex 2 of the mitochondrial electron transport chain; COXIV = cytochrome C oxidase subunit 4; CRF = cardiorespiratory fitness; CS = citrate synthase; Drp-1 = dynamin-related protein 1; ECAR = extracellular acidification rate; ETS = electron transport system; Ex-SPPB = expanded short physical performance battery; FSS = fatigue severity scale; HE = hypoxic exercise, exercise in 12% O_2; high-ALT = high-altitude trekking; HIF-1α = hypoxia-inducible factor-one subunit alpha; HIIT = high-intensity interval training; HR = heart rate; LDH = lactate dehydrogenase; low-ALT = low-altitude trekking; MDA = malondialdehyde; Mfn = mitofusin-1; MICT = moderate-intensity continuous training; MitND5 = mitochondrial NADH dehydrogenase subunit 5; MMP = mitochondrial membrane potential; MOB = mitochondrial oxidant burden; mtROS = mitochondrial reactive oxygen species; MTT = 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide; MVIC = maximal voluntary isometric contraction; N/R = data relevant to review not reported; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; NO = nitric oxide; NRF1 = nuclear respiratory factor 1; NRF2 = nuclear respiratory factor 2; OCR = oxygen consumption rate; OMA1 = Metalloendopeptidase OMA1, mitochondrial; OPA1 = OPA1 mitochondrial dynamin like GTPase; OXPHOS = oxidative phosphorylation; PBMC = peripheral blood mononuclear cells; PGC-1α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGC-1β = peroxisome proliferator-activated receptor beta; PPARα = peroxisome proliferator-activated receptor alpha; PPARγ = peroxisome proliferator-activated receptor gamma; ROS = reactive oxygen species; RS = repeated cycling sprints; RSA = repeated sprint ability (running); RSH = repeated-sprint training in hypoxia; RT = resistance training; SD = standard deviation; SDH = succinate dehydrogenase; SIH = sprint-interval training in hypoxia; SRC = spare respiratory capacity; tAT = time to anaerobic threshold; Tfam = transcription factor A, mitochondrial; UCP2 = uncoupling protein 2; UCP3 = uncoupling protein 3; VE = minute ventilation; VE_{max} = minute ventilation at maximal exercise; VCO_2 = volume of carbon dioxide expired per unit time; VCO_{2max} = maximal volume of carbon dioxide expired per unit time; VO_2 = volume of oxygen consumed per time unit; V_t = ventilatory threshold; $Watts_{max}$ = cycling power at maximal exercise; YYIR2 = yo-yo intermittent recovery test level 2.

Author(s), Year	Table 8: Key Findings - Reports Evaluating Effects of Physical Fitness			
	Cell Number, Proportion, and Phenotype	**Metabolic Regulation**	**Metabolic Function**	**Cell Function**
Reports examining apparently healthy individuals				
Alley JR, Valentine RJ, Kohut ML, 2022 (1)	No difference # naïve $CD4^+$ & $CD8^+$ T cells b/w groups	(N=7/group) Active naïve $CD8^+$ T-cell mitochondrial mass > Inactive (d = 0.76) Naïve $CD4^+$ & $CD8^+$ T-cell MMP, and $CD8^+$ T-cell mitochondrial biogenesis not different b/w groups +Correlation Naïve $CD4^+$ & $CD8^+$ T-cell mitochondrial mass vs. EE (r = 0.41, p = 0.024 & r = 0.36, p = 0.048); effect abrogated when controlled for sex or %BF +Correlation Naïve $CD8^+$ T-cell mitochondrial mass vs. VO_{2peak} (r = 0.47, p = 0.009); effect abrogated when controlled for %BF -Correlation Naïve $CD8^+$ T-cell mitochondrial mass vs. %BF (r = -0.43, p = 0.017)	(N=7/group) ECAR and mitochondrial OCR not different between groups	N/R
Antunes BM et al., 2020[a] (3)	No difference %monocyte subsets Low-fit vs. High-fit	High-fit LPS-induced (100 ng/mL) monocyte PPARγ expression > Low-fit High-fit monocyte PGC-1α expression > Low-fit all treatments (η^2 = 0.513) Low-fit monocyte AMPK expression > High-fit all treatments (η^2 = 0.372)	N/R	Low-fit LPS-induced (100 ng/mL) monocyte IL-10 > High-fit (p = 0.08)
Dorneles GP et al., 2021[a] (20)	N/R	High-fit & Moderately-fit Con-A (10 μg/mL) stimulated mitochondrial membrane depolarization < Low-fit	N/R	Low-fit unstimulated and Con-A (5 ug/mL) stimulated ROS production > Moderately-fit & High-fit High-fit unstimulated and Con-A (5 ug/mL) stimulated proliferation < Moderately-fit & Low-fit
Janssen JJE et al., 2022[b] (34)	No difference # PBMC b/w groups High-fit $\%CD14^+$ monocytes, $CD4^+CD25^+$ & $CD4^+CD25^+CD127^+$ T cells > Low-fit	N/R	High-fit basal OCR, Max OCR, SRC, ATP-linked OCR, proton leak > Low-fit High-fit Con-A (25 μg/mL) stimulated basal & maximal OCR > Low-fit No group difference in Unstimulated, Pre- vs. Post-Exercise, or Con-A (25 μg/mL) stimulated PER	N/R
Mota MP et al, 2010 (50)	N/R	HF lymphocyte mitochondrial H_2O_2 < LF (Y, A, M)	LFY lymphocyte CI activity > HF (Y,A) but no difference LFM vs. HFM -Correlation LF lymphocyte CI activity vs. age (r = -0.47, p-value N/R) LFY lymphocyte CI activity > LFM No difference HFY vs. HFM lymphocyte CI activity	N/R
Reports examining apparently healthy individuals and those with disease				

Pendergast DR et al., 2004[g] (53)	N/R	N/R	No difference leukocyte FA oxidation Inactive vs. Non-elite Runners Elite Runner resting leukocyte FA oxidation > Inactive & Non-Elite Runners CPT2 def. leukocyte FA oxidation < all other groups MS, ED, OB leukocyte FA oxidation = Sedentary CFS leukocyte FA oxidation > Sedentary	N/R
Vladutiu GD et al., 2002 (69)	N/R	N/R	CPT2-def. leukocyte FA oxidation < Sedentary, Trained Trained leukocyte FA oxidation > Sedentary +Correlation leukocyte FA oxidation vs. VO_2 @ RER = 1.0 (r = 0.94, p-value N/R)	N/R
Reports examining individuals with overweight or obesity				
Farinha JB et al., 2015 (22)	N/R	N/R	No difference Active vs Inactive in PBMC CI & CII activity, PBMC non-mitochondrial metabolic activity	Active PBMC ROS, SOD activity, and CAT activity > Inactive
Tyrell DJ et al., 2015 (67)	N/R	N/R	+Correlation PBMC SRC & maximal OCR vs. Ex-SPPB score (r = 0.59, r = 0.58), grip strength (r = 0.54, r = 0.52), knee extensor strength (r = 0.60, r = 0.60), leg skeletal muscle quality (SRC only) (r = 0.56) +Correlation PBMC basal respiration vs. knee extensor strength (r = 0.51) -Correlation PBMC SRC, maximal respiration, basal respiration vs. plasma IL-6 (r = -0.55, r = -0.58, r = -0.61)	N/R

Notes: a = results relevant to this review taken from a single phase of larger study. b = fitness effect data from larger study. Abbreviations: A = Adult group; AMPK = AMP-activated protein kinase; ATP = adenosine triphosphate; %BF = body fat percentage; b/w = between; CI = complex 1 of the mitochondrial electron transport chain; CII = complex 2 of the mitochondrial electron transport chain; CAT = catalase; CFS = individuals with chronic fatigue syndrome; Con-A = concanavalin A; CPT2 def.= individuals with genetic carnitine palmitoyltransferase 2 deficiency; ECAR = extracellular acidification rate; ED = individuals with eating disorder, anorexia nervosa; EE = energy expenditure; Ex-SPPB = expanded short physical performance battery; FA = fatty acid; HF = high-fitness group; HFA = high-fit adult group; HFM = high-fit middle-aged adult group; HFY = high-fit young adult group; IL-"X" = interleukin-"X"; LF = low-fitness group; LFA = low-fit adult group; LFM = low-fit middle-aged adult group; LFY = low-fit young adult group; LPS = lipopolysaccharide; M = Middle-aged adult group; MMP = mitochondrial membrane potential; MS = individuals with Multiple Sclerosis; N/R = data relevant to review not reported; OB = individuals with obesity; OCR = oxygen consumption rate; OXPHOS = oxidative phosphorylation; PBMC = peripheral blood mononuclear cells; PER = proton efflux rate; PGC-1α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ = peroxisome proliferator-activated receptor gamma; RER = respiratory exchange ratio; ROS = reactive oxygen species; SOD = superoxide dismutase; SRC = spare respiratory capacity; TNF = tumor necrosis factor; VO_2 = volume of oxygen consumed per time unit; VO_{2peak} = peak volume of oxygen consumed per time unit; Y = Young adult group.

Supplementary Table 1 – Review of Potentially Overlapping Review Articles			
Title	Subject	Overlap	Not Overlap
Immunmetabolism-fit: How exercise and training can modify T cell and macrophage metabolism in health and disease. (PMID: 35452394)	Review of phenotypic and metabolic features of T cells and macrophages, as well as what is known regarding their response to exercise	Clear topic overlap	Narrative review, not systematic Limited to T cells and macrophages
Influence of Obesity and Weight Loss on the Bioregulation of Innate/Inflammatory Responses: Macrophages and Immunometabolism (DOI: 10.3390/nu14030612)	Review of inflammatory dysregulation in obesity, concept of bioregulation of innate immunity (i.e., regulation of inflammatory potential via exercise), speculation regarding whether nutritional interventions can offer similar effects via weight loss	Regulatory role of exercise on immune function, with emphasis on metabolism	Limited to innate immunity Narrative review
Costly immunometabolic remodelling in disused muscle buildup through physical exercise (DOI: 10.1111/apha.13782)	Review of skeletal muscle and systemic consequences of atrophy and potential for exercise to rectify maladaptive changes	Use of exercise to remediate maladaptive immunometabolic changes with inactivity	Narrative review focused on the problem of muscle atrophy due to inadequate loading, and potential solutions to this problem
Type and Intensity as Key Variable of Exercise in Metainflammation Diseases: A Review (DOI: 10.1055/a-1720-0369)	Review of the effects of exercise and training on monocytes and lymphocytes (T-cells) in people with Obesity/MetS/ Diabetes	Effects of acute and chronic exercise on monocyte and lymphocyte bioenergetics	Narrative review focused on people with obesity/MetS/ Diabetes Limited focus on cellular metabolism
Does Modern Lifestyle Favor Neuroimmunometabolic Changes? A Path to Obesity (DOI: 10.3389/fnut.2021.705545)	Discussion of the impact of sedentary lifestyle and poor diet on systemic inflammation, and how this translates to neuroinflammation	Relationship between lifestyle, energy substrate use, inflammation	Perspective piece, anchored in the role of neuro-inflammation on path to obesity
Exercise and the Adrenergic Regulation of Immunity (DOI: 10.1016/j.bbi.2021.07.010)	Effects of exercise and training on mobilization of leukocytes and the role of adrenergic signaling in this process. Potential for exercise to modulate adrenergic signaling and improve responses to stress.	Effects of catecholamines on immunometabolism could yield some overlap	Narrative review focused on adrenergic signaling rather than exercise immuno-metabolism
Immunometabolic responses according to physical fitness status and lifelong exercise during aging: New roads for exercise immunology (DOI: 10.1016/j.arr.2021.101341)	Summary of adverse immunometabolic consequences of aging and inactivity, verified and potential benefit effects of exercise	Immunometabolism in aging and obesity, influence of exercise on these relationships	Narrative review with emphasis on the effects of aging specifically Effects of acute versus chronic exercise not well segregated
Mitochondrial Functionality in Inflammatory Pathology – Modulatory Role of Physical Activity (DOI: 10.3390/life11010061)	Review of maladaptive changes to systemic inflammation and OS with aging and metabolic disease, discussion of exercise effects on macrophages via mitochondrial signaling, implications towards mitigating systemic inflammation and compromised immune function	Effects of exercise on circulating monocytes and resident macrophages	Narrative review focused on mitochondrial signaling within macrophages
Endurance Exercise Mitigates Immunometabolic Adipose Tissue Disturbances in Cancer and Obesity (DOI: 10.3390/ijms21249745)	Review of the adverse adipose tissue changes in obesity and effects of exercise on modulating tissue inflammation in obesity and cancer	Effects of exercise on leukocyte metabolism and phenotype in adipose tissue	Focus on the effects of exercise on adipose tissue in the context of obesity and cancer Emphsis on cytokine and cell subset effects
SARS-CoV-2 and mitochondrial health: implications of lifestyle and aging (DOI: 10.1186/s12979-020-00204-x)	Influence of immune cell mitochondrial function on overall immune function, necessity of hormesis to maintain mitochondrial function	Lifestyle effects on mitochondrial health, implications to immune function	Not review of exercise effects on immune cell metabolism
Muscle-Organ Crosstalk: Focus on Immunometabolism (DOI: 10.3389/fphys.2020.567881)	Review of muscle-organ signaling, as modified by exercise and training. Short discussion of role(s) for myokines in immunometabolism.	Muscle-derived signaling molecules (myokines) that mediate effects of exercise throughout the body	Review of interorgan signaling via myokines, not focused on the effects of exercise on immune cell metabolism

Impact of Exercise on Immunometabolism in Multiple Sclerosis (DOI: 10.3390/jcm9093038)	Review of adverse immunometabolic changes in MS, potential for exercise to induce an anti-inflammatory state, and future research directions for the use of exercise in MS patients	Immunometabolic changes due to exercise that lead to an anti-inflammatory bias	Strictly limited to context of MS
Exercise of immunometabolic regulation in Cancer (DOI: 10.1038/s42255-020-00277-4)	Effects of exercise on organ systems that participate in carcinogenesis and on the TME.	Changes in cell phenotype and cytokine production associated with exercise	Exercise effects on metabolism and exercise effects on immune system discussed separately
Exercise immunology: Future directions (DOI: 10.1016/j.jshs.2019.12.003)	Summary of data from field of exercise immunology to date, potential utility of immunmetabolic outcome measures with examples from recent data	Discussion of both the effects of exercise on immunity and the role of cellular metabolism in directing immune cell form and function.	Cellular metabolism relates current state of the science and future directions for research rather than literature review
The Exercise Training Modulatory Effects on the Obesity-Induced Immunometabolic Dysfunctions (DOI: 10.2147/DMSO.S234992)	Review of adverse metabolic and immune changes in obesity with emphasis on monocyte recruitment and macrophage polarization, and how exercise may ameliorate or exacerbate meta-inflammation	Exercise effects on cytokine gene expression patterns and the number and phenotype of circulating cells	Emphasis on the pathogenesis and pathological consequences of obesity-induced chronic inflammation
New Insights about Regulatory T Cells Distribution and Function with Exercise: The Role of Immunometabolism (DOI: 10.2174/1381612826666200305125210)	Review of impact of exercise on circulating regulatory T cell numbers and functions, with implications towards combatting systemic inflammation. Particular consideration is given to how metabolic changes associated with exercise training may be affecting regulatory T cell function.	Metabolic stimulus of exercise and its potential effects on regulatory T cell number and function Role of cellular metabolism in regulatory T cell function	Limited to discussion of regulatory T cells
Nutrients, immune system, ad exercise: Where will it take us? (DOI: 10.1016/j.nut.2018.09.019)	Discussion of innate and adaptive immune-cell metabolism and how cellular metabolism can be affected by exercise and nutrients	Effect of exercise on metabolic signaling in immune cells plus its impacts on cell differentiation	Narrative review
Immunometabolism: A Multi-Omics Approach to Interpreting the Influence of Exercise and Diet on the Immune System (DOI: 10.1146/annurev-food-032818-121316)	Presentation of immunometaboilsm as a framework for integrating multiple analytical techniques to assess the acute and chronic effects of exercise on the immune system.	Effects of exercise on immune cell number and functional measures	Heavy emphasis on metabolomics and immuno-nutrition, less emphasis on cellular metabolism
Macrophage Polarization: Implications on Metabolic Diseases and the Role of Exercise (DOI: 10.1615/CritRevEukaryotGeneExpr.2016015920)	Review of the role of macrophages in metabolic diseases and inflammation, effects of exercise on macrophage polarization	Effect of exercise on macrophage gene expression and metabolism via cell polarization	Limited to macrophages Emphasis on metabolic disease

Supplementary Table 2: List of Potentially Relevant References Excluded from Analysis with Reason for Exclusion				
Article title	Journal	Authors	Year	Reason for exclusion
The Effects of Mitochondrial DNA Deletion and Copy Number Variations on Different Exercise Intensities in Highly Trained Swimmers	Cellular and Molecular Biology	O. Baykara, S.K. Sahin, F. Akbas, M. Guven, I. Onaran	2016	Does not meet review independent variable criteria (participant not adults)
Peripheral Blood Mononuclear Cells Antioxidant Adaptations to Regular Physical Activity in Elderly People	Nutrients	C. Busquets-Cortés et al.	2018	Does not meet review independent variable criteria (no exercise or physical fitness component)
Molecular choreography of acute exercise	Cell	K. Contrepois et al.	2020	Does not meet review dependent variable criteria (no leukocyte energy metabolism data)
Antioxidant Regulatory Mechanisms in Neutrophils and Lymphocytes After Intense Exercise	Journal of Sports Sciences	M.D. Ferrer, P. Tauler, A. Sureda, J.A. Tur, A. Pons	2009	Does not meet review independent variable criteria (participants not adults)
Alpha-Lipoic Acid Supplementation Increases the Efficacy of Exercise- and Diet-Induced Obesity Treatment and Induces Immunometabolic Changes in Female Mice and Women	The Federation of American Societies for Experimental Biology Journal	S. Le Garf et al.	2020	Does not meet review dependent variable criteria (insufficient data regarding effect of exercise specifically)
Effects of 6-Week Specific Low-Intensity training on Selected Aerobic Capacity Parameters and HSPA1A, HSPB1, and LDHb Gene Expression in High-Level Rowers	Genetics and Molecular Research	Z. Jastrzebski, M. Zychowska	2015	Missing data
The effect of mitochondrial energetics inhibitors on spontaneous rosette formation of lymphocytes from athletes	Journal of Sports Medicine and Physical Fitness	J.I. Karpova, E.N. Mokhova, N.I. Volkov	1987	Does not meet review dependent variable criteria (no leukocyte energy metabolism data)
Cycling Exercise Training Enhances Platelet Mitochondria Bioenergetics in Patients with Peripheral Arterial Disease: A Randomized Controlled Trial	Thrombosis and Haemostasis	M.L. Lin et al.	2021	Does not meet review dependent variable criteria (no leukocyte energy metabolism data)
Immune adaptation to chronic intense exercise training: new microarray evidence	BMC Genomics	D. Liu et al.	2017	Does not meet review dependent variable criteria (data from whole blood, not leukocytes)
No Effect of Resveratrol in Patients with Mitochondrial Myopathy: A Cross-over Randomized Controlled Trial	Journal of Inherited Metabolic Disease	N. Lokken et al.	2021	Does not meet review dependent variable criteria (insufficient data for unique exercise effect)
Affected pathways and transcriptional regulators in gene expression response to an ultra-marathon trail: Global and independent activity approaches	PLOS One	M. Maqueda, E. Roca, D. Brotons, J.M. Soria, A. Perera	2017	Does not meet review dependent variable criteria (data from whole blood, not leukocytes)
Sixteen-Week Physical Activity Intervention in Subjects With Increased Cardiometabolic Risk Shifts Innate Immune Function Towards a Less Proinflammatory State	Journal of the American Heart Association	M.P. Noz et al.	2019	Does not meet review independent variable criteria (physical activity, not exercise data)
Moderate to vigorous physical activity volume is an important factor for managing nonalcoholic fatty liver disease: A retrospective study	Hepatology	S. Oh et al.	2015	Does not meet review independent variable criteria (physical activity, not exercise data)

Influence of Cardiorespiratory Fitness on PPARG mRNA Expression Using Monozygotic Twin Case Control	Journal of Diabetes Research	M.R. Queiroga et al.	2015	Does not meet review independent variable criteria (participant adults)
Genomic signatures of a global fitness index in a multi-ethnic cohort of women	Annals of human genetics	E. Rampersaud et al.	2013	Does not meet review dependent variable criteria (data from whole blood, not leukocytes)
Mitochondrial reactive oxygen species generation in blood cells is associated with disease severity and exercise intolerance in heart failure patients	Nature- Scientific Reports	R. Shirakawa et al.	2019	Does not meet review independent variable criteria (comparisons by disease status, not exercise or physical fitness)
Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity	Journal of Translational Medicine	R.C.W. Vermeulen, R.M. Kurk, F.C. Visser, W. Sluiter, H.R. Scholte	2010	Does not meet review independent variable criteria (comparisons by disease status, not exercise or physical fitness)
High-Intensity Interval Training Improves Mitochondrial Function and Suppresses Thrombin Generation in Platelets Undergoing Hypoxic Stress	Nature- Scientific Reports	L.-H. Wu, S.-C. Chang, T.-C. Fu, C.-H. Huang, J.-S. Wang	2017	Does not meet review dependent variable criteria (no leukocyte energy metabolism data)
Do Blood Cells Mimic Gene Expression Profile Alterations Known to Occur in Muscular Adaptation to Endurance Training?	European Journal of Applied Physiology	J. Zeibig, H. Karlic, A. Lohninger, R. Dumsgaard, G. Smekal	2005	Does not meet review independent variable criteria (participant adults)