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Are there benefits from the use of fish oil supplements in athletes? A systematic review

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Abstract

Despite almost 25 years of fish oil supplementation (FS) research in athletes and widespread use by the athletic community, no systematic reviews of FS in athletes have been conducted. The objectives of the systematic review are to: 1) provide a summary of the effect of FS on the athlete's physiology, health and performance; 2) report on the quality of the evidence; 3) document any side effects as reported in the athlete research; 4) discuss any risks associated with FS use; 5) provide guidance for FS use and highlight gaps for future research. Electronic databases (PubMed, EMBASE, Web of Science, Google Scholar) were searched up until April 2019. Only randomised placebo-controlled trials (RCTs) in athletes, assessing the effect of FS on a health, physiological/biochemical, or performance variable were included. Of the 137 papers identified through searches, 32 met inclusion criteria for final analysis. Athletes varied in classification from recreational to elite, and from Olympic to professional sports. Mean age for participants was 24.9 ± 4.5 years, with 70% of RCTs in males. We report consistent effects for FS on reaction time, mood, cardiovascular dynamics in cyclists, skeletal muscle recovery, the pro-inflammatory cytokine TNF-alpha, and post-exercise nitric oxide responses. No clear effects on endurance performance, lung function, muscle force or training adaptation were evident. Methodological quality, applying the PEDro scale, ranged from 6 to a maximum of 11, with only four RCTs reporting effect sizes. Few negative outcomes were reported. We report various effects for FS on the athlete's physiology; the most consistent findings were on the central nervous system, cardiovascular system, pro-inflammatory cytokines, and skeletal muscle. We provide recommendations for future research and discuss the potential risks with FS use.

Keywords: performance; injury; inflammation; mood state; recovery; DHA; EPA; exercise

1.0 Introduction

The effects of fish oil supplementation (FS) on athlete health and performance have been researched for the past ~25 years. The early research focused on the potential of FS to modify the inflammatory response to exercise. However, subsequent studies have investigated the effects of FS on metabolism, the immune response, and the respiratory and cardiovascular, musculoskeletal, or central and peripheral nervous systems, with most recent research exploring the effect of FS on neuronal injury.

Docosahexaenoic acid (DHA, C22:6n-3) and eicosapentaenoic acid (EPA, C20:5n-3) are the long chain polyunsaturated omega-3 (n-3) fatty acids present in FS. They are natural constituents of seafood including algae, crustaceans and fish, and to much a lesser extent dairy and meat (the diet of the animal influencing the n-3 fatty acid content). In addition to both dietary intake (e.g. eating fish) and FS changing n-3 fatty acid status, endurance training is known to alter skeletal muscle membrane composition, leading to changes in the muscle phospholipids including increasing DHA content and decreasing the n-6/n-3 fatty acid ratio (1,2). By virtue of training, athletes may acquire a "superior" n-3 fatty acid status compared to the non-athlete and therefore have less need to use supplements. For example, endurance training alters muscle DHA content significantly (1). Therefore, dietary requirements for the specific long chain n-3 fatty acids may differ in athletes, both collectively in terms of recovery and performance effects, or individually for the respective fatty acids. EPA and DHA have been reported to have differential effects on the antioxidant systems and anabolic-catabolic pathways in skeletal muscle (3,4). Moreover, EPA has inhibitory effects on cyclooxygenase-2 expression, and metabolism of arachidonic acid (an n-6 fatty acid) (5). Furthermore, EPA is the precursor for 3 series prostanoids and 5 series leukotrienes (eicosanoids), whilst DHA is the precursor for protectins and maresins, with both fatty acids producing the anti-inflammatory and pro-resolving, aptly named resolvins (5).

Case studies have demonstrated that elite athletes use FS (6,7). A recent review focussing on nutritional recovery strategies in team sports athletes concluded there was emerging evidence for n-3 fatty acid supplementation (the studies referenced used FS) to support recovery in season (8).

However, the American College of Sports Medicine position statement on nutrition and athletic performance (9), whilst comprehensive, provides no statement or guidance on the use of FS (9). According to the International Olympic Committee's recent consensus statement on dietary supplements, there is "limited support" for FS in modifying inflammation and reducing upper respiratory tract infections, and whilst low risk, it is "unclear if FS should be pursued by athletes" (10). A lack of consensus for FS in athletes is evident within the literature.

FS use constitutes a billion-dollar industry, in which growth has been exponential, with the fish oil market expected to reach USD 5 billion by 2025 if trends continue (11). Concerns have been raised however, over the quality of some fish oil products (12,13). Furthermore, FS are marketed by sports nutrition manufacturers specifically for the athlete, varying in formulation, and it is well recognised that nutritional supplements are not without risk for the athlete (10). To our knowledge no systematic review of FS in athletes has been conducted to date, despite numerous publications, including many narrative reviews. A systematic review of the evidence is warranted. In this review we will focus specifically on FS (EPA and DHA) in relation to the athlete. The aims of this systematic review are to: 1) provide a summary of the effect of FS on the health and performance of athletes; 2) report on the quality of the evidence; 3) document any side effects as reported in the athlete research; 4) discuss any risks associated with FS; 5) provide guidance for FS use and highlight gaps for future research.

2.0 Methods

2.1 Search strategy

The preferred reporting for systematic reviews and meta-analysis protocols (PRISMA) checklist was followed. Figure 1 summarises the study selection process. Electronic searches were performed up until April 2019 with no date restrictions in PubMed, EMBASE, Web of Science, and Google Scholar using the search terms "athlete" and "omega-3", and "athlete" and "fish oil" with the terms being included in the study title, abstract and/or keywords. To ensure the search strategy captured all relevant studies, searches within the electronic databases were conducted under each of the following specific terms (cognition, performance, injury, recovery, adaptation, skeletal muscle, muscle soreness,

endurance, strength) and the following methods were applied to the searches: in PubMed, MESH headings were used and combined, while in EMBASE, Emtree was used with the expansion of the subject search term with the subject added to query builder. Reference lists of individual study publications and reviews were consulted for additional studies. The publication abstracts and titles were screened individually to ensure removal of studies not meeting the inclusion/exclusion criteria. If there was any doubt over article inclusion or exclusion, the paper was obtained in full for clarification. The remaining publications were obtained in full, with each author independently reviewing the screened papers according to the inclusion and exclusion criteria.

2.2 Eligibility criteria for studies

Only publications written in the English language were included. Due to the plethora of research papers on FS, we focussed on studies in which the research participants were characterised as male or female *athletes*, whether recreational, well-trained or elite athletes. We chose not to include research on healthy physically active individuals and extrapolate such findings to athletes a) due to the known effects of training on increasing muscle phospholipid n-3 fatty acid content (1); b) in order to summarise the evidence for practitioners in sport settings; and c) in order to identify gaps in the literature as they pertain to the athlete. Only randomised placebo-controlled trials (RCTs), assessing the effect of FS on a health, and/or physiological/biochemical or performance variable were included. For example, studies that did not include a matched control or placebo group were excluded (14-16)(6,7), as were non-randomised trials (17). Publications which failed to report fully the methodology and statistical approach in full were excluded (18,19), as were studies where the participants were not classified as athletes (i.e. recreationally or physically active, or resistance trained were excluded) (20-30). Figure 1 summarises the studies excluded. To ensure we captured a broad spectrum of FS studies, no restrictions were imposed on sport, sex of participants, fish oil dose, duration of FS, whether supplements were EPA or DHA only, or lack of reporting of dietary or blood n-3 fatty acid status, or whether FS was combined with other ingredients (e.g. antioxidants). The latter point is relevant because these are the products which make it to market and are used by athletes. We

chose to extract and tabulate separately both the statistically significant and non-significant findings, given the wide range of outcomes and variables assessed (Tables 1-4).

2.3 Assessment of study quality and risk of bias

Studies were rated using the Physiotherapy Evidenced Database scale (PEDro) https://www.pedro.org.au/english/downloads/pedro-scale/, an 11-point validated scale for the assessment of RCTs. Any differences of opinion regarding the rating of study quality were resolved between authors.

2.4 Data synthesis and extraction

A meta-analysis was not conducted due to the heterogeneity across studies and the variety of outcomes reported. Data extraction captured information relating to (a) study design (e.g. randomised, placebo controlled trial); (b) sample characteristics (e.g., age, sample size, sex, sport, athlete status); (c) health and performance variables (e.g., mood, cognition and skill, cardiovascular and respiratory, skeletal muscle, immune and inflammation, biomarkers, physical performance); (d) fish oil dose and dosing period; (e) additions to the fish oil (e.g., vitamin D, vitamin E etc); (f) measurement of n-3 fatty acid biomarkers (e.g. plasma EPA and DHA); (g) non-significant effects and findings.

3.0 Results

3.1 Study selection and sports

We identified a total of 137 papers using our search strategy, of which 32 RCTs (level of evidence 1B) met the inclusion criteria (Figure 1). The mean sample size of included studies was 27 participants (range 15-81 participants).

The 32 RCTs were grouped into the following areas (some studies represented twice); oxidative stress only (n=5), immunity, inflammation and oxidative stress (n=10), muscle recovery (n=5), team sports and training adaptation (n=5), cardiovascular physiology (n=5), cognition and mood state (n=4), respiratory health (n=2) and injury related (n=2) (Tables 1-4). Only significant findings are reported in the results and discussed. However, tables 1-4 provide a summary of both the significant and non-significant findings.

3.2 Subject characteristics

The majority of investigations (n=22) studied men only. Nine RCTs included participants of both sexes, and one RCT included women only. The mean age for participants in the FS and placebo groups across the RCTs was 24.9 ± 4.5 years; one RCT failed to report the age of the participants (31). Athletes varied in classification, from recreational (e.g. non-competitive) to elite (elite referring to a professional or national level competitive standard) and from a range of summer Olympic sports (e.g. judo, swimming, cycling, marathon) and professional sports (i.e. American football, soccer, rugby, Australian Rules football and basketball) (Tables 1-4).

3.3 Methodological quality and risk of bias

The methodological quality of the RCTs, applying the PEDro scale (maximum score obtainable 11), ranged from a score of 6 (2 studies) to a maximum of 11 (1 study), with an average score of 9. Of the 32 RCTs included, 25 (75%) were double-blind in design, seven (20%) were single-blind, and three incorporated a cross-over design with a wash out period ranging from 2-weeks to 35 days (32-34). A major methodological flaw affecting 28 of the 32 RCTs (88%), was that the size of the treatment effect (i.e. effect sizes) was not reported. Sponsorship and research funding by the fish oil industry was clearly reported in seven RCTs.

Seventeen studies (53%) measured various biomarkers of n-3 fatty acid status in order to confirm compliance with the FS. Only one RCT ensured subjects were matched at baseline for n-3 fatty acid status, thus reducing the potential confounding effect of different baseline status on outcome (35) .

3.4 Main findings

The findings were analysed and grouped in relation to the main outcomes assessed. Inflammation was the most frequently studied variable in athletes (19,36-44), with doses of EPA ranging from 300 to 2400 $mg \cdot day^{-1}$, and of DHA from 400 to 1500 $mg \cdot day^{-1}$. For the majority of pro- and anti-inflammatory mediators measured, the effects were inconsistent: for example, despite the

197 variation in the timing of blood sampling and source of the cytokines, IL-6 (measured at rest) showed
198 a reduction in four RCTs (19,39,42,43) and an increase in one RCT (37), with no effect at rest or post-
199 exercise in three RCTs (40,42,43). However, there was evidence in four out of the five RCTs, for an
200 effect of FS on attenuating the production of TNF-α by peripheral blood mononuclear cells (PBMCs)
201 in ex vivo culture (37,38,42,43). Only one RCT reported on upper respiratory tract illness (URTI), via
202 an illness log and questionnaire, in which a moderate dose of fish oil reduced the total number of
203 symptom days, but not the number of URTI episodes, symptom severity score or URTI duration;
204 however, the FS included vitamin D, whey protein and 100 kcal more energy than the control group
205 condition (41).
206 Muscle recovery and team sport training adaptations were examined across seven RCTs
207 (Table 3). Four RCTs reported positive effects on measures of recovery (e.g. muscle soreness, counter
208 movement jump, creatine kinase activity) (45-48), a single RCT noted a positive effect on anaerobic
209 endurance in soccer players but not on a battery of other physiological measures (35), whilst two
210 RCTs reported no effect on physiological adaptations and performance (49,50). Overall effects were
211 consistent for muscle recovery, but inconsistent for training adaptation and performance outcomes in
212 team sport athletes. The RCT with the largest change in plasma n-3 fatty acids (240%) with FS did
213 observe effects on subjective and objective measures of recovery in professional rugby players (46).
214 The two RCTs using the same FS in a recovery product formulation (i.e. administered post-training
215 with whey protein), reported positive effects on muscle recovery (46,47)
216 Positive effects of EPA and DHA at various doses were observed on cardiovascular and
217 oxygen kinetics in all studies of cyclists (cycling efficiency, maximum oxygen uptake ($\dot{V}O_{2max}$))
218 (32,51,52) but there were no improvements in endurance performance (e.g. time trial (51)); see Table
219 4. An effect on endurance was not observed in the two RCTs of individuals involved in team sports
220 (49,50), or in athletes from four summer Olympic sports (48).
221 Three RCTs with various doses of EPA and DHA showed FS increased biomarkers of lipid
222 peroxidation (i.e. malondialdehyde, F_2-isoprostanes) at rest (19,53,54), and four RCTs reported this
223 post-exercise (53-56) (Table 1). Two RCTs showed the post-exercise effect for FS on increasing F_2-

isoprostanes was prevented with the addition of various antioxidants (54,56). Antioxidant enzyme activity (i.e. superoxide dismutase, glutathione peroxidase, glutathione reductase) was increased with FS in three RCTs (19,44,57), and decreased in two RCTs (42,43). Finally, three RCTs showed an effect on increasing nitric oxide post-exercise (32,53,54) (Table 1).

Of the studies assessing cognitive variables, a positive effect on reaction time and mood state was seen across all RCTs where measured (n=4), regardless of sport and ability i.e. professional rugby (46), soccer (58), athletics (33), and karate (59) (Table 4).

Few studies have examined injury risk. A positive effect for DHA was observed on biomarkers of neuronal injury (31), and a single RCT incorporating high doses of both EPA and DHA showed an effect on tendinopathy pain and subsequent activity level (60) (Table 3). Three RCTs explored the effect of FS on respiratory function (Table 4), one of which examined the effect of FS on exercise induced bronchoconstriction (EIB) (34). The RCT reporting positive findings in EIB was of the highest methodological quality score (11 out of 11). In healthy athletes, a positive effect for FS on lung function was identified in one RCT in wrestlers (61), but this was not corroborated when examined in soccer players (35) .

3.5 Adverse effects and product analysis

Of the included RCTs, only one reported on adverse effects with FS (DHA use only), citing poor palatability, gastrointestinal distress and nausea in a small number of participants (~10%); (31). Three RCTs reported the laboratory analysis of the FS and thus verification of the product contents (31,50,52) with analysis independent of the manufacturer in just two studies (31,50). No RCTs reported on FS analysis confirming the absence of traces of banned substances in the batches studied, which is relevant for the elite athlete participants.

4.0 Discussion

4.1 Summary of key findings

We present the first systematic review of FS in athletes. We report evidence from a number of RCTs for an impact of FS upon the athlete's physiology. The most consistently reported findings to date relate to skeletal muscle recovery, post-exercise nitric oxide response, biomarkers of lipid peroxidation, tumour necrosis factor alpha (TNF-α) production by immune cells and cardiovascular dynamics in cyclists. Inflammation was the most studied variable in athletes, with FS modifying various inflammatory markers at rest and post-exercise (via immune cell activation), with a consistent effect on attenuating the production of TNF-α by PBMCs. No effects on endurance performance, muscle force, or training adaptation were evident across sports. Few negative outcomes were reported. Where relevant, we will contextualise findings from studies in athletes with the inclusion of research published in non-athletes and conclude with recommendations for future research and guidance for practitioners in sport.

4.2 Cardiovascular and performance effects in endurance athletes

DHA is preferentially increased in skeletal muscle phospholipids in response to training (2), whilst both EPA and DHA are incorporated into mitochondrial phospholipids with FS (62). We found evidence for a consistent effect of FS on advantageously modifying cardiovascular physiology and whole-body oxygen consumption in athletes. A mechanism for this effect could be related to the capacity for DHA and EPA to moderate sympathetic activation of blood vessels and blood flow, via the expression and activation of endothelial nitric oxide synthase and production of nitric oxide (NO) (63). Indeed, three RCTs reported an effect for FS on increasing NO. Nevertheless, effects for FS on aerobic performance were not evident. Furthermore, the positive findings extended only to controlled laboratory studies in cyclists. Indeed, FS consistently showed no effect on tests of endurance undertaken in competitive and professional team sport athletes. It is possible that greater intra- and inter-subject variability for performance tests may have confounded the findings. Finally, a recently published review article on the effects of FS on performance (encompassing both sedentary and athletic populations) was in agreement with our findings; an effect for FS in endurance-based athletes on oxygen efficiency, but no clear effects on performance (92).

280 4.3 Muscle recovery and adaptation

281 The research into muscle recovery in athletes has been focussed on a greater dose of EPA vs.
282 DHA administered, with one study showing that EPA, but not DHA, stimulates muscle protein
283 synthesis in the presence of leucine and inhibits muscle protein breakdown in muscle cell culture (4).
284 We identified seven RCTs investigating muscle recovery and training adaptation, in which differences
285 in FS formulations and types of sport participation may account for divergent findings. For example,
286 the positive effects on muscle soreness (i.e. perceived), damage (i.e. creatine kinase activity) and
287 recovery (i.e. counter movement jump peak force) were evident in professional rugby and competitive
288 soccer players when administered over several weeks, in which the FS also included vitamin D and
289 whey protein (46,47). This was notwithstanding the fact that the control groups in both studies
290 received matched timed protein and carbohydrate intakes. In addition, the 3-week FS study in
291 Olympic athletes showing an effect on fatigue (i.e. % drop in Wingate power), also included vitamin
292 D (48). It is conceivable, that the strongest effects for FS on accelerating muscle recovery may be
293 most evident when administered alongside other nutrients known to impact on skeletal muscle
294 remodelling (i.e. vitamin D, whey protein) as part of a recovery drink. The strength of the evidence
295 for FS on enhancing adaptations to training in team sport athletes is very weak, with three RCTs
296 reporting no effect on performance (47,49,50), and just one observing an effect for FS on increasing
297 anaerobic capacity over 4 weeks of training (35). An effect of FS on muscle force (maximal voluntary
298 contraction) was absent across all RCTs. Three separate RCTs of recreational, competitive and
299 professional athletes reported an effect for FS on neuromuscular performance measures e.g. muscle
300 activation, Wingate power, counter movement jumps (45,46,48). Further research is needed to clarify
301 the effect of FS on the neuromuscular system, and whether EPA is more effective for enhancing
302 muscle recovery *in vivo*, given the effects on muscle recovery which were seen using a 1:1 ratio of
303 EPA and DHA.

304

305 4.4 Respiratory function

306 Exercise induced bronchoconstriction (EIB) causes narrowing of the airways leading to
307 decrements in pulmonary function and is well known to adversely affect elite athlete performance.

Inflammation is part of the pathophysiology of EIB, and as such FS has been tested as a non-pharmacological therapeutic treatment option. FS reduced the post-exercise decline in forced expiratory volume, systemic inflammation and bronchodilator use in elite athletes (34). However, the evidence for an effect of FS on modifying lung function in healthy athletes without EIB is weak, with only one RCT showing benefit after 12 weeks of FS (61). In short, FS may reduce airway inflammation in elite athletes with EIB and may be considered as an adjunctive non-pharmacological low risk treatment option; clearly further research is needed to better understand the effects of FS on respiratory function. However, the absence of EIB is likely to limit the potential application of FS on respiratory function.

4.5 Inflammation and immunity

For the healthy athlete, the evidence summarised in Table 2 suggests that FS may modify the PBMC inflammatory response, when assessed through changes in cytokines e.g. TNF-α (36-38,42,43). However, we acknowledge the conflicting evidence with regards to immunomodulation in athletes; with differences in study design (e.g. pre- vs. post-exercise sampling), training and immune function status, n-3 fatty acid dose, measures of immunity, and the underlying fatty acid status affecting the consistency of study outcomes (19,36-38,40,42-44,64). In contrast to our findings, a systematic review published in 2012 reported that moderate n-3 fatty acid consumption (900-2000 mg day^{-1}) does not lead to changes in inflammatory biomarkers in healthy non-athletes (65), suggesting a differential effect between trained and untrained individuals. The biological material sampled and thus the source of the cytokines (e.g. plasma vs in vitro (ex vivo) assessments of immune cell function), the timing (at rest vs post-exercise) and dose of n-3 fatty acids are critical factors in determining consistency of study outcomes with regards to inflammation. Finally, complicating the findings, using modest doses (400 mg day^{-1} EPA and DHA) combined with polyphenols such as green tea and quercetin and administered during an intensified period of training, Nieman et al. (39) showed an anti-inflammatory effect (i.e. a reduction in high sensitivity C-reactive protein and IL-6 vs placebo) both at rest and post-exercise (39). Since antioxidant supplements may modify adaptive responses to exercise (66), caution should be applied to their use.

We did not find any convincing evidence that FS provided protection from illness. Of the ten RCTs exploring the effects of FS on immune and inflammatory variables in athletes, only one RCT included data on infectious symptoms and illness (41). FS in combination with 10 ug vitamin D_3 and 8 g whey protein reduced the number of illness symptom days. Further research is needed to corroborate these findings.

4.6 Cognition

We observed consistent findings for an effect of FS on aspects of cognition and mood state in athletes, namely reaction time, using combinations of EPA and DHA (33,46,58,59). Improvements in reaction times related to working memory and episodic memory using DHA (67), and complex reaction times with EPA (68) have also been reported in healthy male and female non-athletes. Furthermore, higher red blood cell DHA levels are associated with improved working memory performance and are predictive of baseline performance (69). Thus FS, with an emphasis on DHA, could be anticipated to improve mood states and cognitive performance in athletes, in which mental tasks requiring more complex cortical processing are likely to benefit the most; as may athletes with poor n-3 fatty acid status prior to FS (e.g. low red blood cell DHA, bottom quartile omega-3 fatty acid index). Mechanisms by which FS may modify brain function and therefore mood (e.g. vigour and fatigue), include the increased incorporation of DHA into neuronal membranes leading to alterations in membrane fluidity and speed of signal transduction and neurotransmission (70), and via neuroprotective and antidepressant-like effects in the face of a physiological stress as observed with FS in rodents (71). Decreased n-3 fatty acid status has been reported in chronic fatigue patients vs healthy controls (72).

4.7 Injury

Tendinopathy

FS as a means of treating tendinopathy in athletes in conjunction with pharmacological therapy has been previously proposed (73). We identified one positive clinical trial in athletes, which reported a reduction in pain with FS compared to the placebo (99% vs. 31%; $p<0.001$), and greater

increases in voluntary sporting activity (60). Two FS trials in non-athletes have been published and are discussed (74): in contrast to the findings of Mavrogenis et al. (60) in athletes, Roe et al. (74) using the same FS supplement found no effect for the FS vs placebo when administered to patients (n=55) with unilateral epicondylitis (i.e. tennis elbow) over several months. Neither study assessed the participant's underlying n-3 fatty acid status. In a recent multi-centre clinical trial (n=73), Sanford et al. (75) recruiting patients with unilateral shoulder pain, found no significant difference between FS (EPA 1530 $mg \cdot day^{-1}$ plus DHA 1035 $mg \cdot day^{-1}$) vs placebo in the primary outcome measure (the Oxford shoulder score). However, the FS group experienced a more rapid improvement from baseline to 3 months, and a modest effect ($p<0.05$) on shoulder pain and disability, flexion and abduction at 3, but not 2, 6 or 12 months, and strength at 12 months. More patients in the placebo group were using analgesic medication ($p=0.02$). Moreover, a significant relationship between increasing plasma EPA and DHA and reduction in pain was reported. An effect of DHA and EPA on tendinopathy may result from alterations in the formation of specialised pro-resolving mediators (SPMs) leading to alterations in pain and inflammatory signalling. For example, in arthritis patients taking FS, plasma SPMs were negatively correlated with erythrocyte sedimentation rate, and synovial fluid resolvin E2 (RvE2) was negatively associated with pain score (76). Thus, at present the evidence for an effect of FS is inconclusive; however, in lieu of the above and the reported minimal side effects, FS may provide a non-pharmacological low risk means of supporting tendinopathy rehabilitation in athletes, exerting a modest dose- and n-3 fatty acid status dependent effect.

Concussion and head trauma

We identified only one publication in American football (31), a sport well recognised for having a high incidence of concussions (77). The RCT was designed to test the effects of DHA (3 different DHA dosing strategies) on neuronal injury across a playing season in NCAA Division 1 American football players (n=81). The authors demonstrated that FS (DHA only) attenuated the rise in neurofilament light (NFL; a biochemical marker of axonal injury that is observed to rise across the playing season in American football players). Caution should be exercised with regards to dosing

391 strategies for DHA, given the lowest dose used (2000 mg day^{-1}) was the most effective. Further work
392 in other sports which present with a high incidence of concussion is clearly warranted.
393
394 *Surgery and rehabilitation*
395 FS are sometimes prescribed to elite athletes following surgery (7) and, despite the emerging
396 role of resolvins, protectins and maresins in inflammatory control and resolution, no RCTs have
397 examined the effects of FS on wound healing in athletes post-surgery. Of relevance, FS (1660 mg·day^{-1}
398 EPA and 1100 mg·day^{-1} DHA) administered to healthy young subjects failed to enhance wound
399 closure at any of the time points examined after initiation of the wound in comparison to the placebo
400 (78). Research in healthy animals corroborates these findings, with FS and linseed (a source of plant
401 n-3 fatty acids but not EPA and DHA) delaying the percentage wound closure and re-epithelisation
402 compared to controls at 14 days post wound (79). In contrast, obese diseased and therefore 'inflamed'
403 animals display enhanced wound healing with an n-3 fatty acid rich 'high fat' diet vs controls, and n-6
404 and saturated fat rich diets (80). Given the lack of supportive scientific evidence in athletes or indeed
405 healthy young participants, caution is advised over the use of FS in otherwise healthy athletes
406 recovering from acute surgery or an acute traumatic injury (with the exception of neuronal injury and
407 the use of DHA and the correction of any underlying n-3 fatty acid deficiency). The decision of
408 whether to use FS for rehabilitation purposes, is further complicated by the findings of recent
409 experimental research utilising a non-surgical unilateral limb immobilisation approach (no actual
410 injury or wound and therefore no activation of an immune inflammatory response). FS prevented
411 muscle disuse atrophy in non-athletes, preserving both muscle mass and mitochondrial respiration
412 (81,82).
413
414 *Bone health*
415 Bone stress injuries are common injuries sustained by athletes (83), and interventions that can
416 mitigate the risk are warranted. There have been no RCTs in athletes that examined the effects of FS
417 on bone metabolism, or bone mineral density. However, the National Aeronautics and Space
418 Administration (NASA) agency conducted a series of research studies from cell culture to human

interventions in association with bed rest and space flight, in order to assess the potential for FS to ameliorate bone loss, with an effect for n-3 fatty acids (84). Those astronauts who ate more n-3 fatty acid rich fish experienced less of a decline in bone mineral density as a result of short duration space flight. Moreover, a higher intake of n-3 fatty acids (i.e. fish intake) was associated with reduced bone resorption (measured via N-telopeptide) with bed rest in non-athletes (84). In conclusion, a higher fish intake and better n-3 fatty acid status may serve to protect against bone loss. Speculatively this might also allow attainment of a higher bone mineral density for the athlete. However, research in athletes would clearly be needed to support this hypothesis.

4.8 Adverse effects of FS

Only one RCT reported adverse effects of FS, in which the athlete complaints were mild and affected a small proportion (~10%). Thus, given the wide range of FS used, doses administered and time frames, FS appears to be safe in athletes. The most commonly stated concerns with regards to the use of chronic high doses of FS are: 1) increased oxidative stress, driven by oxidation of the polyunsaturated fats in FS; 2) a hypocoagulant effect; 3) exposure to heavy metals and toxins concentrated in the oils; and 4) mild gastro-intestinal side effects such as nausea. Each area will be briefly discussed below. Table 1 provides a summary of the RCTs studies measuring the effect of FS on oxidative stress in athletes, with or without added nutrients. Based on these studies in athletes, FS use increases lipid peroxidation at rest and post-exercise compared to a placebo or control (53,54); however, the increase in oxidative stress post-exercise is prevented when FS are consumed with antioxidant nutrients e.g. polyphenols and/or vitamins (54-56). In addition, three RCTs report an effect for FS on increasing nitric oxide post-exercise (32,53,54). It should be noted that well-designed human studies examining the effect of FS on intracellular antioxidant enzymes and systems, have found ~3 weeks of FS increases the expression and activity of antioxidant enzymes (85). Others have reported differential effects for the fatty acids, EPA and DHA, on muscle antioxidant enzymes (3).

Anecdotally, athletes sometimes consume supplements in excess of recommendations, in accordance with the “more is better” mantra. Excessive FS doses over a prolonged period of time may pose an increased risk of bleeding. For example, an amateur athlete consuming 20 g a day of n-3 fats

447 from supplements presented with a duodenal ulcer and bleeding (86). A recent systematic review
448 including 52 publications incorporating data on both healthy and surgical patients, concluded that FS
449 reduces platelet aggregation in healthy subjects; however, there is no increased risk of bleeding during
450 or after surgery with FS in RCTs (87). The European Food Safety Authority (88) scientific opinion
451 states "Long-term supplemental intakes of EPA and DHA combined up to about 5 $g \cdot day^{-1}$ do not
452 appear to increase the risk of spontaneous bleeding episodes or bleeding complications, or affect
453 glucose homeostasis, immune function or lipid peroxidation, provided the oxidative stability of the n-
454 3 long chain polyunsaturated fatty acids is guaranteed". Athletes should be educated to avoid
455 excessively high doses of FS. Overall, we are not aware of any RCTs in which FS exerted a negative
456 outcome on performance or recovery. Furthermore, mild gastrointestinal side effects (belching,
457 nausea, fishy taste) in the studies reviewed were rare occurrences.
458
459 4.9 Quality of FS products
460 Only two studies sought independent laboratory analysis of the FS used, which is somewhat
461 concerning given that nine studies were conducted in elite athletes, and a further two in semi-
462 professional athletes. A number of studies from different countries have raised concerns over both the
463 quantity and the quality of the fatty acids contained within various commercial products (12,13,89).
464 For example, in the USA, Kleiner et al. (12) found that over 70% of the supplements analysed (47 FS
465 products were selected) did not contain the amounts of EPA and DHA stated on the product label.
466 Moreover, a study in New Zealand, identified just 3 of 32 supplements contained quantities of EPA
467 and DHA that were 100% or over of the label content. Two thirds contained less than 69% of label
468 claimed content (13). Of greater concern is the finding that 83% of supplements exceeded levels of
469 peroxide markers, with 50% exceeding recommended total oxidation values calculated (13). Only 3
470 supplements met international recommendations. Such results are not without controversy however,
471 with the analytical methods in the latter study (13) receiving criticism from industry scientists (90). In
472 fact, in an industry-sponsored study, all 10 fish oil products met international guidelines (90). In
473 summary, care needs to be taken when recommending FS products for athletes, and ideally the

474 products should not only be analysed from an anti-doping perspective, but also for the presence and
475 concentration of heavy metals, dioxins, and polychlorinated biphenyls.
476
477 5.0 Study limitations and bias
478 Only randomised placebo-controlled trials were included in the review in order to minimise
479 selection bias associated with the non-randomisation of participants. However, our initial search
480 strategy captured six non-randomised and/or non-placebo controlled studies in athletes
481 (14,15,17,35,64,91) which may offer further insight into this field albeit without the same scientific
482 rigour. We included both single (20%) and double-blind (80%) studies however, and thus there is a
483 risk of bias due to the lack of blinding of researchers in the single blind studies. Removing the seven
484 single-blind studies (32,36,38,41,49,54,59) does not change the conclusions, however it weakens the
485 strength of the findings for inflammation, since two single-blind studies reported on TNF-α (36,38),
486 and on post-exercise NO (32,54).
487 With regards to the specific FS characteristics, some included additional nutrients; stated in
488 the tables 1-4. Such studies were not excluded from the review. In fact, by including studies with
489 additional nutrients (e.g. antioxidants), an effect for antioxidants on attenuating lipid peroxidation was
490 observed. Furthermore, FS sold into the marketplace contain various antioxidants (i.e. alpha-
491 tocopherol or carotenoids) in order to reduce oxidation of the fatty acids, ensuring greater product
492 stability, and to prolong the product's shelf life. The inclusion of such studies gives the review
493 ecological validity.
494
495 **6.0 Conclusion**
496 We provide a summary on FS research in athletes (tables 1-4), which demonstrates broadly positive
497 effects and serves as a resource for practitioners. Indeed, FS exert positive effects on cognition,
498 cardiovascular dynamics in cyclists, and muscle recovery. FS also attenuate pro-inflammatory cell
499 responses and may increase lipid peroxidation and post-exercise nitric oxide. An effect for FS on
500 endurance exercise performance was absent across all studies. We are not aware of any RCTs that
501 have demonstrated a negative effect of FS on performance, and the reported side effects with FS use

are mild. Many of the RCTs which report positive effects have used doses of FS that are achievable through the consumption of oily fish. It is recommended that future research on FS and n-3 fatty acid rich diets should measure biomarkers of n-3 fatty acid status, in order to allow the proper investigation and understanding of the impact of n-3 fatty acid status and the dose response on outcomes. Furthermore, FS research is needed in athletes to further understand the impact on neuromuscular performance, bone metabolism, rehabilitation from injury (e.g. surgical vs. non-surgical outcomes including bone stress), EIB, risk of illness, and risk of sudden cardiac death in athletes (93) with high vs. low n-3 fatty acid status. Finally, future FS studies should include effect sizes and have the supplement analysed for contaminants and the supplement contents verified independently from the manufacturer.

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Table 1. Summary of studies of fish oil supplementation (FS) in athletes relating to oxidative stress.[1]

Author	Sport	Athlete status	Sex and sample size	Biomarkers affected by FS	Dosing period (weeks)	Active treatment (mg^{-1} day)	Omega-3 biomarker response to FS	No effect for FS[2]
Zebroswka et al. (32)	Cycling	Competitive	Male participants n =13	↑ NO at rest and post-exercise	3	1320 EPA 880 DHA	Not measured	Endothelium independent vasodilatation, peak power, TGs, LDL and HDL cholesterol, total cholesterol, HR, SBP, DBP, Glycerol, TAS, PWV
Filaire et al. (53)	Judo	Elite	Male participants n = 20	↓ TGs, ↑ MDA at rest only, ↑ MDA, Rmax, CDmax post-ex, ↑ NO post-ex	6	600 EPA 400 DHA	Not measured	GPx
Filaire et al. (54)	Judo	Elite	Male participants n = 28	↑ MDA, Rmax, CDmax at rest, & ↓ post-ex.	6	600 EPA 400 DHA Vitamin C, vitamin E, β-carotene	Not measured	
Filaire et al. (54)	Judo	Elite	Male participants n = 28	↑ MDA, Rmax, CDmax at rest & post-ex., ↑NO post-ex	6	600 EPA 400 DHA	Not measured	
McAnulty et al. (56)	Cycling	Competitive	Male and female participants n = 48	↑ F2-Isoprostane post-ex	6	2000 EPA 400 DHA	↑ Plasma DHA (55.8%), EPA (61.5%)	
McAnulty et al. (56)	Cycling	Competitive	Male and female participants n = 48	Prevented F2-Isoprostane ↑ post-ex	6	2000 EPA 400 DHA Vitamins, minerals, antxs	↑ Plasma DHA (95.3%), EPA (77.8%)	
McAnulty et al. (55)	Cycling	Competitive	Male and female participants n = 39	Prevented F2-Isoprostane ↑ post-ex	2	220 EPA 180 DHA Vitamin C, EGCG, Quercetin, B vitamins.	Not measured	ORAC, ferric reducing ability of plasma
Martorell et al. (57)	Soccer	Semi-Professional	Male participants n = 15	↑ RBC SOD & GRd activity, ↓ GPx	5 days per week for 8 wk	1140 DHA CHO, proteins, almonds	↑ RBC DHA (26.4%)	RBC MDA, carbonyl index, nitrotryosine, CAT
Ghiasvand et al. (19)	Basketball	Well-trained	Male participants n = 34	Resting: ↑ MDA	6	2000 EPA	Not measured	No change TNF-α

1. Key: CAT = catalase; CDmax = maximum amount of conjugated dienes; CK = creatine kinase; DHA = docosahexaenoic acid; DBP = diastolic blood pressure; FO = Fish oil; EGCG = epigallocatechin 3-gallate; EPA = eicosapentaenoic acid; GPx = glutathione peroxidase; GRd = glutathione reductase; HDL = high density lipoprotein HR = heart rate; LDL = low density lipoprotein MDA = malondialdehyde; NO = nitric oxide; ORAC = oxygen radical absorption capacity; PWV = pulse wave velocity RBC = red blood cell; Rmax = maximum rate of oxidation during the propagating chain reaction; SBP = systolic blood pressure; sIgA = salivary immunoglobulin; SOD = superoxide dismutase; TNF-α = tumour necrosis factor alpha; TGs = triglycerides
2. All non-significant findings for the effects of FS

11 Table 2. Summary of studies of fish oil supplementation (FS) in athletes relating to immunity and inflammation[1].

Author	Sport	Athlete status	Sex and sample size	Biomarkers affected by FS	Dosing period (wk)	Active treatment (mg^{-1} day)	Omega-3 biomarker response to FS	No effect for FS[2]
Andrade et al. (36)	Swimmers	Elite	Male participants n = 20	Resting: ↑ PBMC, ↓ Plasma PGE2, ↓ interferon-γ	6	950 EPA 500 DHA	↑ Plasma total ómega-3 fatty acids (45.4%), EPA (196%), DHA (96%)	PBMC TNF-α, IL-2, IL-4, Cortisol, insulin
Delfan et al. (37)	Paddlers	Elite	Male participants n = 22	Resting PBMCs: ↓ TNF-α, ↓ IL-1B, ↑ IL-6, ↑ IL-10, ↓ interferon-γ	4	2400 EPA 1200 DHA	Not measured	IL-4, Th1/Th2 ratio
Santos et al. (38)	Marathon	Competitive	Male participants n = 21	Resting: ↑ Lymphocyte proliferation; ↓ IL-2, ↓ TNF-α, ↓ IL-10; Post-race ↑ Lymphocyte proliferation	8.5	300 EPA 1500 DHA	Not measured	Lymphocyte death. Post-race lymphocyte: IL-2, IL-4, TNF-α, IL-10
Nieman et al. (40)	Cyclists	Competitive	Male and female participants n = 23		6	2000 EPA 400 DHA	↑ Plasma EPA (311%), DHA (40%)	Total blood leukocytes, CK, CRP, ratio sIgA to protein, myleoperoxidase, IL-6, IL-8, IL-1ra, endurance performance
Da Boit et al. (41)	Athletic, non-specific	Recreational	Male and female participants n = 30	Total number of symptom days ↓	16	550 EPA 550 DHA Whey protein, vitamin D	Not measured	URTI incidence, severity and duration of URTI, visits to Medical Doctor, sIgA conc. & secretion rate
Capo et al. (42) (43)	Soccer	Semi-Professional	Male participants n = 15	↓ Post-ex MIP1-α. Post-ex LPS-stimulated PBMCs: ↓ TNF-α, ↓ IL-6, ↓ TLR-4 protein levels. ↑ PBMCs UCP-3, ↓ GPx	5 days per week for 8 wk	1140 DHA CHO, proteins, almonds	↑ RBC DHA (36%)	Oxidative damage in PBMCs, ROS production by PBMCs. Resting and post-exercise plasma: IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-gamma, TNF-α, IL1α, IL-1β, TNF-β, EGF, IL-5, IL-15, MCP-1, GMCSF
Capo et al. (44)	Soccer	Semi-Professional	Male participants n = 15	Resting: Neutrophil gene expression (IL-8, NFkβ); ↑ Neutrophil total MPO, ↑ Neutrophil total CAT activity	5 days per week for 8 wk	1140 DHA CHO, proteins, almonds	↑ RBC DHA (36%)	Neutrophils: Nitrate, nitrite; nitric oxide; MPO, TNF-α, gene expression (COX2, TNF-α, MPO)
Nieman et al. (39)	Cyclists	Competitive	Male and female participants n = 39	Resting: Serum ↓ CRP, plasma IL-6, total leukocytes, Granulocyte oxidative burst ↓	24 days	400 EPA 400 DHA EGCG, Quercetin	Not measured	Plasma IL-10, IL-1ra, TNF-α, CK, MCP, MPO, sIgA protein, HSP-70

Ghiasvand et al. (19)	Basketball	Well-trained	Male participants n = 34	Resting: ↓ IL-6, ↑ GPx	6	2000 EPA Vitamin E +/-	Not measured	No change GPx in EPA-only group

1. Key: 9α11β-PGF2 = prostaglandin metabolite; CAT = catalase; CHO = carbohydrate; CK = creatine kinase; CMJ = counter movement jump; COX2 = cycloxygenase-2; CRP = C-reactive protein; DHA = docosahexaenoic acid; EGCG = epigallocatechin 3-gallate; EGF = epidermal growth factor; EPA = eicosapentaenoic acid; HR = heart rate; FEV1 = forced expiratory volume; IFN-gamma = interferon gamma; IL = interleukin; LTE4 & LTB4 = leukotrienes; GPx = glutathione peroxidase; GMCSF = granulocyte macrophage colony stimulating factor; HSP-70 = heat shock protein 70; MIP1-a = macrophage inflammatory protein-1-α; NFkβ = nuclear factor-kappa-beta; MPO = myeloperoxidase; MCP1 = monocyte chemotactic protein-1; sIgA = salivary immunoglobulin; TGs = triglycerides; TNF-α = tumour necrosis factor alpha; PBMC = peripheral blood mononuclear cell; POMS = profile of mood states; TLR4 = toll like receptor-4; VEGF = vascular endothelial growth factor; VO_2 = oxygen uptake; UCP-3 = mitochondrial uncoupling protein 3; URTI = upper respiratory tract illness
2. All non-significant findings for the effects of FS

Table 3. Summary of studies of fish oil supplementation (FS) in athletes relating to recovery and injury[1]

Author	Sport	Athlete status	Sex and sample size	Mood & Cognition & Skill	Cardiovascular & Respiratory	Skeletal Muscle	Biomarkers	Physical Performance	Dosing period (wk)	Active treatment (mg^{-1} ·day)	Omega-3 biomarker response to FS	No effect for FS[2]
Jakeman et al. (45)	Athletes	Recreational	Male participants n = 27					>Recovery of CMJ	<1	7500 EPA 500 DHA	Not measured	Muscle soreness, CK, IL-6
Lewis et al. 48)	Summer Olympic Sports	Competitive	Male participants n = 31					↓ Fatigue (% drop Wingate power), ↑ VL EMG	3	375 EPA 510 DHA Vitamin D	Plasma EPA ↑ (65.8%), DHA no change	MVC, squat jump, CMJ, back squat, push ups, endurance performance (time trial)
Black et al. (46)	Rugby	Professional-Elite	Male participants n = 20	↓ Fatigue , ↑ Sleep quality		Muscle soreness ↓		↑ Mean CMJ peak force	5	1102 EPA 1102 DHA Whey PRO, CHO, Vitamin D	Plasma omega-3 fatty acids(240%) ↑	
Philpott et al. (47)	Soccer	Competitive	Male participants n = 30			Muscle soreness ↓	↓ CK conc.		6	1102 EPA 1102 DHA Whey PRO, CHO, Vitamin D	Blood omega-3 fatty acids ↑ (58%)	CRP, MVC, soccer passing test, Yo-Yo-Level 2 test
Gravina et al. (35)	Soccer	Competitive	Male and female participants n = 26					↑ Anaerobic endurance (enhanced training effect)	4	4900 EPA 1400 DHA	Blood omega-3 fatty acids ↑ (100%)	Respiratory function (FEV1, FVC), MVC, 20m sprints, vertical Jump height, Yo-Yo-Level 1 test,
Raastad et al. (49)	Soccer	Professional-Elite	Male participants n = 28				↓ TGs		10	1600 EPA 1004 DHA	Plasma EPA (175%), DHA (40%) ↑	VO2max, running speed at anaerobic threshold, run time to exhaustion
Buckley et al. (50)	Aussie Rules	Professional-Elite	Male participants n =25		DBP ↓, sub-max exercise HR ↓		↓ TGs		5	360 EPA 1560 DHA	RBC EPA (116%) DHA (100%), ↑total n-3 (74%)	Run time to exhaustion, VO2/running economy

Oliver et al. (31)	American Football	Competitive	Male participants n = 81		↓ NFL		27	2000-6000 DHA	↑ Plasma DHA (98-99.9%), dose dependant
Mavrogenis et al. (60)	All sports	Recreational	Male participants n = 31	↓ Pain		↑ Activity	32 days	3000 EPA 2112 DHA Vitamins & minerals, GLA	Not measured

1. Key: BP = blood pressure; CHO = carbohydrate; CK = creatine kinase; CMJ = counter movement jump; CRP = C-reactive protein; DBP = diastolic blood pressure; HA = docosahexaenoic acid; EMG = vastus lateralis electromyography recordings; EPA = eicosapentaenoic acid; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GLA = gamma linolenic acid; HR = heart rate; MVC = maximum voluntary contraction; NFL = neurofilament light; RBC = red blood cell; TGs = triglycerides; VL = vastus lateralis; VO_2max = maximum oxygen uptake
2. All non-significant findings for the effects of FS

35 Table 4. Summary of studies of fish oil supplementation in athletes relating to cardiovascular performance, cognition and mood, and respiratory function.[1]

Author	Sport	Athlete status	Sex and sample size	Mood & Cognition & Skill	Immune & Inflammation	Cardiovascular & Respiratory	Skeletal Muscle	Biomarkers	Physical Performance	Dosing period (wk)	Active treatment (mg^{-1} day)	Omega-3 biomarker response to FS	No effect for FS[2]
Raastad et al. (49)	Soccer	Professional -Elite	Male participants n = 28				↓ TGs			10	1600 EPA 1004 DHA	↑ Plasma EPA (175%), DHA (40%)	VO_2max, running speed at anaerobic threshold, run time to exhaustion
Buckley et al. (50)	Aussie Rules	Professional -Elite	Male participants n =25		DBP ↓, sub-max exercise HR ↓		↓ TGs			5	360 EPA 1560 DHA	↑ RBC EPA (116%) DHA (100%), total n-3 (74%)	Run time to exhaustion, VO_2/running economy
Hingley et al. (51)	Runners & Cyclists	Well trained, recreational	Male participants n =26			↓ Sub-max VO_2 during 5 min cycling time-trial				8	140 EPA 560 DHA	↑ OM3I: 4.5% to 6%	Endurance performance (time-trial), Wingate, MVC
Peoples et al. (52)	Cyclists	Competitive	Male participants n = 16			↓ Exercise HR, ↑ cycling economy (↓ sub-max VO_2)				8	800 EPA 2400 DHA	↑ RBC DHA (41.4%), total n-3 (24.3%),	
Zebroswka et al. (32)	Cyclists	Competitive	Male participants n =13			↑ VO_2max (+5%), FMD (%)		↑ NO at rest, post-exercise, ↑ glucose and FFA at rest		3	1320 EPA 880 DHA	Not measured	Endothelium independent vasodilatation, peak power, TGs, LDL and HDL cholesterol, total cholesterol, HR, SBP, DBP, Glycerol, TAS, BM, PWV
Fontani et al. (33)	Athletics	Recreational	Male and female participants n = 33	↑ Vigour, attention, ↓ reaction time, anger, anxiety, depression				↓ Homo-cysteine		5	1600 EPA 800 DHA	↓ AA/EPA	
Fontani et al. (59)	Karate	Competitive	Male and female participants n = 18	↑ POMS, ↓ reaction time						3	4800 EPA 2400 DHA policosanol	Not measured	

Guzman et al. (58)	Soccer	Professional -Elite	Female participants n = 34	↓ Complex reaction time					4	3500 DHA	Not measured	
Black et al. (46)	Rugby	Professional -Elite	Male participants n = 20	↓ Fatigue , ↑ Sleep quality			Muscle soreness ↓	↑Mean CMJ peak force	5	1102 EPA 1102 DHA Whey PRO, CHO, Vitamin D	↑ Plasma omega-3 fatty acids (240%)	
Mickleborough et al. (34)	Endurance Sports	Competitive	Male and female participants n = 20		↓ Urinary LTE4 & ↓ 9α11β-PGF2; ↓ plasma LTB4, TNF-α, IL-1β	Improved lung function (FEV1)			3	3200 EPA 2200 DHA	↑ Neutrophil EPA (1206%), but no change DHA	
Tartibian et al (61)	Wrestling	Recreational	Male participants n = 40			↑ FEV1, ↑ FVC, ↑ VC, ↑ MVV, ↑ FEF25–75, ↑ FIV1			12	180 EPA 120 DHA	Not measured	FEV1% and FIV1%
Gravina et al. (35)	Soccer	Competitive	Male and female participants n = 26					↑ Anaerobic endurance	4	4900 EPA 1400 DHA	↑ Blood omega-3 fatty acids (100%)	Respiratory function (FEV1, FVC), MVC, 20m sprints, vertical Jump height, Yo-Yo-Level 1 test

1. Key: 9α11β-PGF2 = prostaglandin metabolite; ASP = aortic systolic pressure; APP = aortic pulse pressure; AP = augmentation pressure; BAD = brachial artery diameter; CHO = carbohydrate; CK = creatine kinase; CMJ = counter movement jump; DBP = diastolic blood pressure; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL = high density lipoprotein; HR = heart rate; FEV1 = forced expiratory volume; FFA = free fatty acids; FMD = flow mediated dilation; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; FEF = forced expiratory flow from 25% to 75%; FIV1 = forced inspiratory volume in one second; LDL = low density lipoprotein; IL = interleukin; IL- β = interleukin 1 beta; LTE4 & LTB4 = leukotrienes; MVV = maximal voluntary ventilation; Nfl = neurofilament light; NO = nitric oxide; OM3I = omega-3 index; POMS = profile of mood states; PRO = protein; PWV = pulse wave velocity; RBC = red blood cell; SBP = systolic blood pressure; sIgA = salivary immunoglobulin; TAS = total antioxidant status; TNF-α; tumour necrosis factor alpha; TGs = triglycerides; VC = vital capacity; VO_2 = oxygen uptake; VO_2max = maximal oxygen uptake
2. All non-significant findings for the effects of FS

46 Figure 1. Flow diagram of study selection criteria; RCT = randomised controlled trial