Exercise-induced effects on inflammatory markers and brain-derived neurotrophic factor in patients with knee osteoarthritis. A systematic review with meta-analysis.

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ABSTRACT

Background: *In the pathogenesis of knee osteoarthritis (KOA), inflammatory mediators play an important role. However, the precise underlying mechanism by which regular exercise therapy (ET) exert effects on the immune system in KOA patients is unknown.*

Objectives: *The aim of this systematic review was to investigate the basal and acute effects of ET on inflammatory biomarkers and brain derived neurotrophic factor (BDNF) in KOA patients.*

Methods: *PubMed, Web Of Science and PEDro were systematically searched for appropriate studies. If possible, a meta-analysis was performed or an approximation of the effect size (ES) was calculated. Risk of bias was scored using the Cochrane ROB 2.0 or ROBINS-I tools.*

Results: *Twenty-one studies involving 1374 participants were included. Fifteen articles focused on basal exercise effects, four on acute effects, and two on both. Biomarker analysis (n=18) was performed in synovial fluid (n=4) or serum/plasma (n=17). A meta-analysis demonstrated that basal CRP was reduced in KOA patients 6-18 weeks weeks after ET (MD: -0.17;95%CI[-0.31;-0.03]), while IL-6 (MD: 0.21;95%CI[-0.44;0.85]), and TNF-α (MD: -0.57;95%CI[-1.47;0.32]), levels did not significantly change. Also, sTNFR1/2 did not change significantly after ET. For other biomarkers, insufficient data were available to perform a meta-analysis. Nevertheless, a low degree of evidence was found for a decrease in IL-6 (ES:-0.596 & -0.259 & -0.513), an increase in sTNFR1 (ES:2.325), a decrease in sTNFR2 (ES:-0.997) and an increase in BDNF (ES:1.412). Locally, intra-articular IL-10 (ES:9.163) increased, and IL-1β (ES:-6.199) and TNF-α decreased (ES:-2.322) after ET. An acute exercise session elicited a myokine response (ES IL-6:0.314), and an increase in BDNF (no ES-data). No inflammatory effect (ES CRP:0.052; ES TNF-α:-0.019 & 0.081) following an acute bout of training was found. However, a single bout of exercise elicited a decrease in intra-articular IL-10 (no ES-data).*

Conclusion: *ET can induce circulatory and intra-articular anti-inflammatory effects in patients with KOA. The anti-inflammatory properties have important implications for informing these patients and clinicians about the underlying effects of ET.*

INTRODUCTION

OA is a multifactorial chronic degenerative disorder, affecting the whole joint. It is mainly characterized by degeneration of articular cartilage, synovitis, and alterations in both peri-articular structures and subchondral bone (31, 36). According to the Global Burden of Disease Study of 2019, more than 527 million people are affected with OA worldwide; with the knee (364,58 million people) and hip (32,99 million people) as the most commonly affected joints (60). Clinically, OA is often associated with pain, joint stiffness, crepitus and loss of function, which can lead to disability over time. OA is one of the leading causes of global disability, accounting for 7.1% of total musculoskeletal disability burden worldwide, which is an increase of 31.4% compared to 2007 (54). This increased global burden can be explained by ageing and obesity (79).

OA has long been erroneously considered as a non-inflam-

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matory arthropathy. However, it is a complex disease in which structural changes are not only caused by mechanical but also by systemic factors, such as inflammation that initiates and/or perpetuates the OA process (10, 93). Once activated by mechanical and/or systemic perturbation, joint cells (e.g. chondrocytes) and the synovial membrane in turn release inflammatory mediators into the joint cavity (73, 77). Pro-inflammatory cytokines are believed to play a pivoting role in the initiation and development of OA, specifically interleukin (IL)-1β and tumor necrosis factor (TNF)-α are key players in this process (61, 73, 77). The pleiotropic cytokine IL-6 is considered to also have a major contribution in the pathogenesis of OA (61, 73). On the other hand, there is evidence that the production of anti-inflammatory cytokines, in particular IL-4 and IL-10, can counteract the OA inflammation process and cartilage matrix degradation (61).

In addition to inflammatory cytokines, brain-derived neurotrophic factor (BDNF) is also involved in inflammatory responses (71). BDNF, a member of the neurotrophic growth factor family, contributes to neuronal development, protection and survival of neurons, and brain plasticity. About 75% of circulating BDNF origins from the brain (25). Other potential sources of BDNF include skeletal muscle, smooth muscle, platelets, endothelial cells, epithelial cells, and peripheral blood mononuclear cells (25). Additionally, BDNF can also be produced by joint cells (i.e. chondroblasts, fibroblasts) (34, 53). It is suggested that inflammation induces BDNF production and in turn, BDNF exerts pro- and/or anti-inflammatory effects in part through modulation of inflammation-related cytokines (71). Furthermore, TNF-α and IL-6 can induce BDNF secretion in human monocytes (82). To date, there are still some gaps in the literature regarding the role of BDNF in the pathogenesis of OA. Previous research reported sixfold higher plasma BDNF levels compared to the synovial fluid BDNF levels in knee osteoarthritis (KOA) patients in the acute stage of joint inflammatory process and there was a positive correlation between plasma BDNF levels and self-reported pain (87).

Exercise therapy is considered the first-choice non-pharmacologic intervention for OA (5, 21, 94). Regular moderate exercises like strength training or walking are known to ameliorate physical functioning and to reduce pain and disability in people with OA (13, 28). However, the mechanisms of action to explain these beneficial effects on pain and function, are not fully understood (78). One of the hypotheses to explain the beneficial effects of exercise is through an anti-inflammatory effect. Nevertheless, the precise underlying mechanism by which regular exercise therapy exert positive effects on the immune system in OA patients is unknown (9).

The immune system can be influenced via exercise through the release of specific signaling molecules, called exerkines, secreted by several tissues throughout the body. One of the first discovered exerkines are the myokines, which are produced by skeletal muscle cells in response to exercise (17). Myokine IL-6 increases in the bloodstream after muscle contraction and stimulates the release of IL-1 receptor antagonist (IL-1RA) and IL-10 by blood mononuclear cells. As such, muscle-derived IL-6 causes anti-inflammatory effects by promoting immune cells to secrete anti-inflammatory cytokines (17, 52). Remarkably, the acute increase of IL-6 during exercise is not preceded by an increase in pro-inflammatory cytokine TNF-α, which is the case in septic or pathologic conditions (52). Furthermore, the acute and chronic exercise-induced effects differ from each other as resting levels of IL-6 are lower in healthy individuals after chronic exercise as compared to healthy untrained individuals. Accordingly, the exercise-induced effect of IL-6 is divers (i.e. pleiotropic) and context dependent (i.e. acute or chronic exercise) (17). A recent review of the literature concluded that in healthy elderly the levels of pro-inflammatory cytokines (i.e. C-reactive protein (CRP), TNF-α, IL-6) were reduced after an exercise intervention program (6). However, these effects were more heterogeneous in elderly with a specific disorder. Additionally, it was suggested that repetitive exercise (i.e. chronic exercise) can influence the secretory profile of blood mononuclear cells, apparently through the release of myokines. This promotes the secretion of anti-inflammatory cytokines and can consequently counteract inflammaging (6).

On the other hand, there are suggestions that myokines also have a role in the communication between muscles and the brain (72). Centrally, exercise-induced effects are most clearly observed in the hippocampus. It has been demonstrated that the volume of the hippocampus increased in healthy humans after aerobic exercises and after a walking intervention in elderly. This can be explained by the function of BDNF, which levels are increased, on cell proliferation (17, 72). BDNF is expressed after exercises and circulatory BDNF is increased after an acute session of aerobic exercises. Whether BDNF is secreted into the circulation by contracting muscle cells is still unclear (41, 72). It seems that the brain is the main source of circulating BDNF during exercise (71). This raises the question whether other molecules are involved -apparently myokines- which are peripherally secreted and reach the brain/hippocampus to stimulate central BDNF production (17, 72). Nevertheless, BDNF derived by contracting muscles has a metabolic effect on the muscle itself as it will stimulate the oxidation of fat and use of glucose (72). In elderly, a meta-analysis demonstrated that an aerobic program had larger effects on the increase in BDNF levels than resistance training, which also supports the hypothesis that muscle derived BDNF is not released into the bloodstream (24, 71). However, no significant increases in BDNF after exercises were demonstrated as compared to non-exercising elderly (24).

Although exercises have positive effects on OA related symptoms (i.e. pain, disability) (42), the underlying working mechanism of physical exercise is not fully discovered (78). A general overview of acute and chronic exercise-induced effects on inflammation and BDNF in KOA lacks in literature, which is needed to further unravel and understand the underlying exercise effects in the KOA population. Therefore, we aim to summarize all relevant and available literature regarding the effects of physical exercise therapy on inflammatory biomarkers and/or BDNF in patients with KOA in this systematic review. As such, important insights can be discovered, stressed and shared with researchers and clinicians to improve therapy effects in the future.

METHODS

The systematic review protocol was registered at PROSPERO (CRD42020162746) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (57).

Information sources
A systematic search was conducted in PubMed, Web of Science and PEDro (last search was performed on May 5th 2021 for all search databases). Additional studies were identified by scanning the reference lists of included articles.

Two reviewers (D.B., E.M.) identified search terms using MeSH vocabulary and text word searching, one reviewer (E.M.) pilot tested the search strategy and discussed afterwards with 2 reviewers (D.B., I.B.) until a final search strategy was developed. Search terms were determined based on PICO dimensions: osteoarthritis (Population), physical exercise (Intervention), inflammatory markers, BDNF (Outcome). The final search strategies can be found in Table 1.

Study selection
Studies had to meet following inclusion criteria:

(1) Studies had to describe the effect of physical exercise on inflammatory markers and/or BDNF.
(2) Randomized controlled trials (RCT), non-randomized controlled trials (NRCT), trials with a pre-experimental design and pilot studies of which a full text was available were included.
(3) Participants of both sexes and any age with OA were considered.
(4) There was no restriction in grade of OA.
(5) At least one exercise intervention had to be investigated in the study. All types of exercise therapy (e.g. aerobic, strength, flexibility,…) were allowed. No restriction was made on duration of intervention and follow-up.

Studies that were written in another language than English, Dutch, German or French were excluded.
Eligibility assessment was independently performed by two reviewers (S.P. and K.L.). Articles were preliminary screened on title and abstract. Thereafter, full texts of the remaining articles were screened, if no sufficient information was provided in the abstract. If needed, authors of the articles were contacted to obtain full texts. Both researchers (S.P and K.L) were not blinded for author details (e.g. names, institution). Disagreements between reviewers were resolved by consensus or by a third independent reviewer (L.L.).

Data collection process
Based on 'The Cochrane Collaboration Data Collection Form' a data extraction sheet was developed by two review authors (D.B. and E.M.) (Supplementary Table 1: Data extraction form). One review author (S.P) extracted the data from the included studies. If necessary, authors of the included articles were contacted by e-mail to obtain specific information (e.g. concerning mean concentrations of inflammatory cytokines, exercise modalities, p-values, 95% confidence intervals (CI)). If authors did not responded, graphs were measured using GetData Graph Digitizer 2.26 (30), were possible, to obtain an estimation of the raw values if they were not published in the article (1, 29, 32, 39, 85, 86).

Risk of bias assessment
The risk of bias was determined by two independent review authors (S.P. and K.L). Conflicts were resolved by a third independent reviewer (L.L.). The risk of bias in RCTs was assessed with 'A revised Cochrane risk of bias tool for randomized trials' (ROB 2.0) (91). The overall risk of bias judgment is classified into three categories, going from low ROB to some concerns, and ending with high ROB. For other study designs than RCTs, the 'Risk of Bias In Non-randomized Studies- of Interventions' (ROBINS-I) (90) was used. Drugs with anti-inflammatory effects, physical activities, health status, nutritional intake, body composition, age and gender were pre-defined as possible confounding factors. Diet, medication and physical activity were pre-specified as potential co-interventions to be taken into account when assessing the risk of bias using ROBINS-I. According to the ROBINS-I tool, the overall ROB judgment is classified into four categories (i.e. low ROB (lowest class), moderate ROB, serious ROB, and critical ROB (highest class)).

Summary measures
The study outcomes were: circulating or intra-articular inflammatory markers and BDNF. To understand the exercise-induced changes in biomarkers, a focus was placed on both acute effects and effects on basal levels. The acute exercise effect was defined as changes in concentrations of biomarkers during and immediately following a bout of exercise (25); i.e. < 24h after an acute bout of exercise (63). The exercise effect on basal levels was defined as changes in concentrations of biomarkers when the acute exercise-induced changes were washed out, e.g. after an overnight resting period (25); i.e. ≥ 24h post exercise (63).

Planned methods of analysis
A meta-analysis was performed when at least two studies investigated the same outcome and inflammatory biomarker. I^2 was calculated to assess heterogeneity, with an I^2 value ≥ 50% being indicative of high heterogeneity, i.e. there is inconsistency among the results of the included studies (40). Subgroup analyses were performed to discover possible reasons of high heterogeneity, if possible (40). Type of exercise therapy, duration of intervention and sampling method were considered for subgroup analyses to reduce heterogeneity. For results that were not incorporated into a meta-analysis, effect-sizes were estimated, where possible. Based on the type of analysis (within or between group), Hedges's gav or Cohen's d effect sizes (ES) were approximated with the assumption of a 0.5 correlation coefficient (55).

Additional analyses
For the meta-analysis of basal effects, mean change from baseline values and standard deviations were used, or calculated when not available (40), for both study groups (i.e. exercise and control group). Mean values were estimated from medians (99), and standard deviations were derived from the standard error and sample size or from the 95% confidence interval (40).

RESULTS

Study Selection
As shown in Figure 1a, the search procedure resulted in 678 unique papers, of which 624 were excluded based on title and abstract. The remaining 54 articles were evaluated full textual, of which 21 articles (1, 3, 4, 7, 29, 32, 33, 38, 39, 47, 51, 58, 59, 65-68, 80, 85, 86, 102) met the inclusion criteria and were finally included.

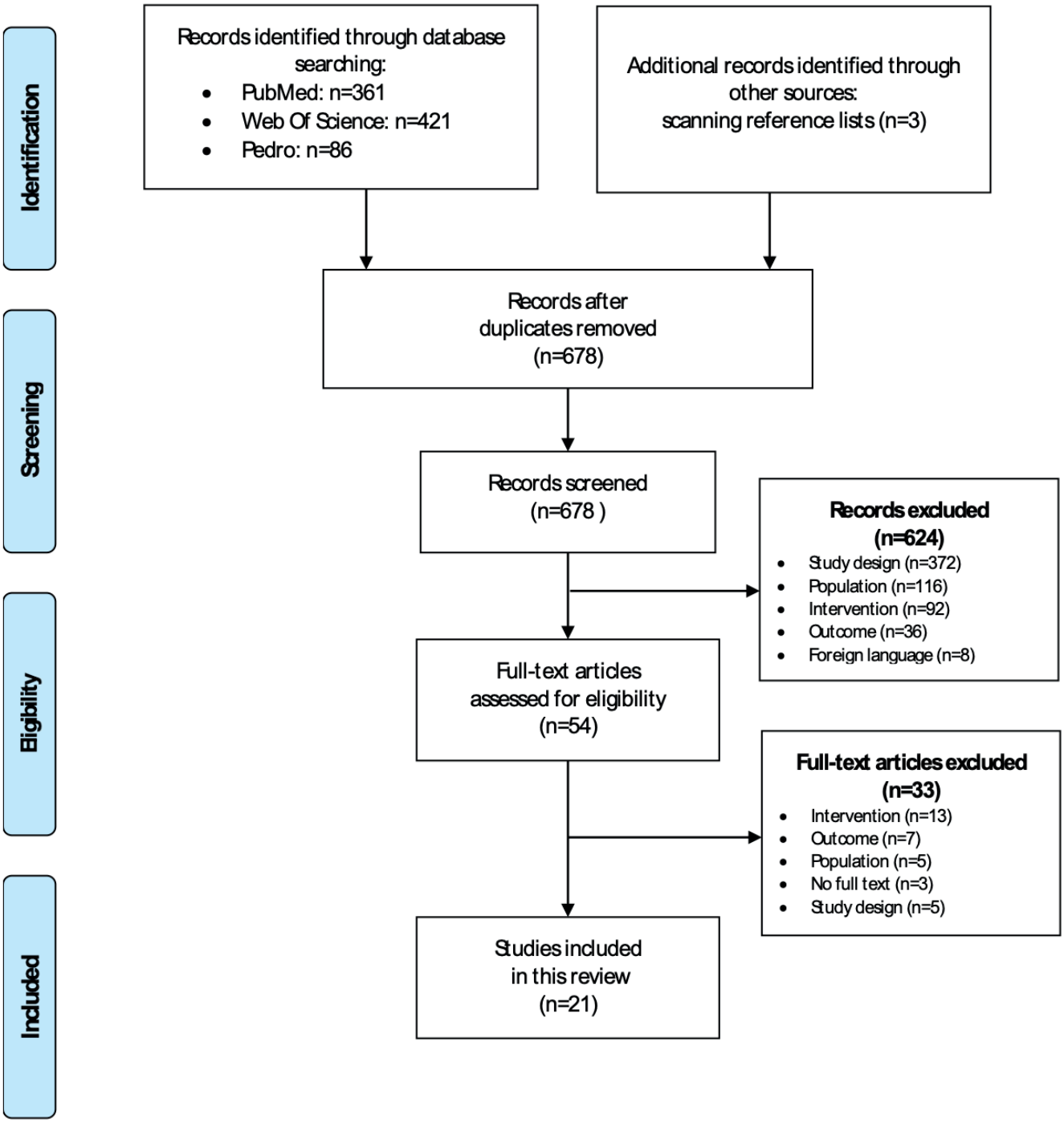

Figure 1a. Flowchart of the study selection

Study characteristics

All included articles were interventional studies (Figure 1b). Fifteen studies were RCTs (3, 4, 7, 38, 51, 58, 59, 65-68, 80, 85, 86, 102) of which two were pilot studies (51, 65). One study was a NRCT (29). Five studies were non-randomized uncontrolled trials (NRUCT) with a pre-experimental design (one group; pre-posttest) (1, 32, 33, 39, 47). Two of them were pilot studies (32, 33). One used a two-phase sequential design (47). Three of the included articles (7, 59, 66) were part of the same trial (64). Two reported on IL-6 (7, 66) while only one reported on CRP (7), and CRP metabolite (CRPM) (59). Therefore, with regard to IL-6, only the results of Messier et al. (66) will be further analyzed in this review as they were only available in detail in this paper.

The included studies involved a total of 1 374 participants, with mean age ranging from 57.57 ± 5.79 years (80) to 75± 7.4 years (85). All studies except two (39, 102) reported on the sex of the participants, as such at least 969 females and 294 males were included in the studies (Table 3) . All 21 articles reported on KOA patients. Only one study also included a healthy control group (i.e. participants without KOA) (29). During the intervention period, at least 287 participants dropped out (in fact several studies did not report the number of blood and/or synovial fluid samples that were acquired during each follow-up and incorporated into the analysis). Supplementary Table 2 provides an overview of all included studies regarding the sample size, number of drop-outs, available samples at each follow-up and how drop-out/data loss was handled in the data analysis.

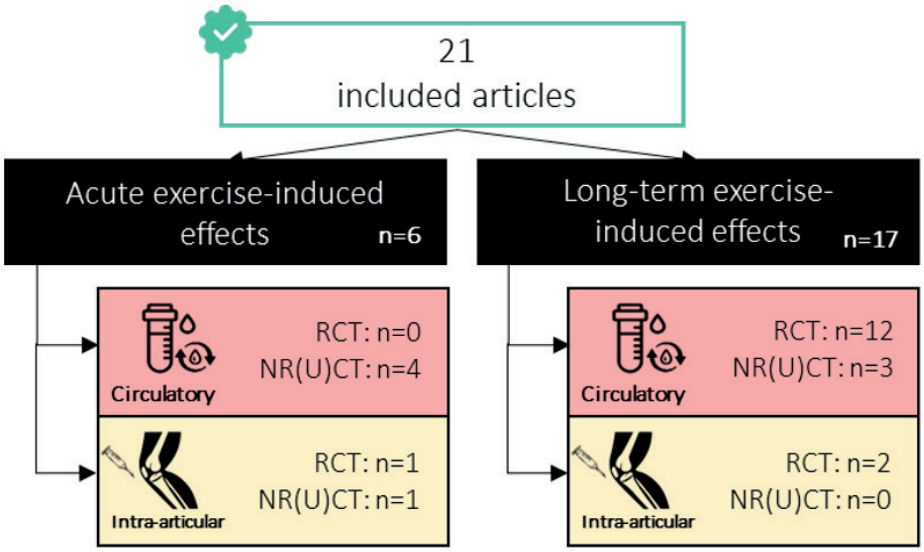

Figure 1b. Overview of the study characteristics. 21 articles were included in this systematic review; 4 focused on acute exercise-induced effects, 15 on long-term exercise-induced effects and 2 on both. A further subdivision of the studies was made based on systemic (i.e. circulatory) or local (i.e. intra-articular) effects, and based on the type of study design.
RCT: randomized controlled trial; NR(U)CT: non-randomized (un)controlled

Eight studies specified overweight and/or obesity as an inclusion criterion (7, 29, 58, 59, 65-68): three articles included patients with body mass index (BMI) between 27 and 40.5 kg/m² (7, 59, 66), three others included patients with BMI ≥ 28.0 kg/m² (65, 67, 68), another article included patients with a BMI ≤ 30.0 kg/m² (58), and one study reported outcomes on 'obese' participants with BMI ranging from 35.9 ± 4.5 kg/m² to 36.2 ± 5.6 kg/m² (29).

Eight articles included KOA patients with a sedentary lifestyle (3, 7, 29, 59, 66-68, 80), three studies included physically active participants (1, 38, 39), and in eight studies physical lifestyle was not defined as an inclusion or exclusion criterion (4, 32, 33, 47, 58, 65, 85, 102). In one study, participants were excluded if they needed a walking aid (86) and in another if they exercised more than 3x/week (51).

The use of anti-inflammatory drugs was handled differently across the studies. In nine studies, medication policy was unclear (1, 4, 32, 33, 47, 51, 67, 80, 86). In four studies, it was allowed to maintain regular medication usage (7, 65, 66, 68). In two of them it was also possible to adjust medication usage during the intervention period (7, 66). In two studies the usage of all pain and anti-inflammatory medication usage was prohibited (38, 39). Five articles reported criteria about gluco-, cortico- or steroid usage (3, 29, 59, 85, 102): in one study, the usage of corticosteroids and/or corticosteroid infiltrations was forbidden (3, 102), in one study glucocorticoids usage was prohibited (85), and in another study steroids were not allowed (29). On the other hand, participants in the study of Loeser et al., 2017, were allowed to use NSAIDs (59). None of the studies adjusted their statistical analysis for concomitant anti-inflammatory drug use.

The included studies were classified into four categories based on the exercise protocols that were investigated: aerobic (n= 5) (3, 32, 33, 47, 80), strength (n=9) (4, 29, 38, 39, 80, 85, 86), aerobic & strength (n=6) (7, 59, 65-68) and other (n=2) (e.g. flexibility training, Tai Chi) (1, 58) (Table 2). Samut et al. compared two types of exercise therapy and was therefore incorporated in both the aerobic and strength category (80).

With regard to the aerobic category, in three studies the exercise intervention consisted of walking (32, 33, 47). In the other study the exercise intervention was cycling and/or swimming (3). In the studies of Gomes et al. 2012 (32) and Gomes et al. 2014 (33), two types of exercise protocols could be distinguished: a training protocol and an acute exercise protocol. The training protocol included a 30 minutes' walk, 3x/week for 12 weeks. The acute exercise protocols of these two studies were identical (walking on a treadmill for 20min with a cool down phase for 30min) (32, 33). The study of Jayabalan et al. (47) consisted of an acute exercise protocol in which participants also had to walk continuously and with intervals of 15 minutes on a treadmill (47). In the exercise phase of the training programs of the included studies in the aerobic group (3, 32, 33, 80) the intensity/load increased progressively during the intervention period. However, small differences are noticeable in training protocols between studies (Table 2).

Exercise protocols of the strength group were more heterogeneous, both in duration of the intervention period and exercise session, intensity/load of the exercises and exercise modality (see Table 2).

In the aerobic & strength category, the exercise protocol of the studies of Beavers et al., 2014 (7), Loeser et al., 2017 (59) and Messier et al., 2013 (66) were the same; as well, the exercise protocol of the studies of Miller et al., 2004 (67) and Nicklas et al., 2004 (68) were identical as they were part of respectively the Intensive Diet and Exercise for Arthritis (IDEA) trial and Arthritis, Diet, and Activity Promotion Trial (ADAPT) study. The exercise protocols of the IDEA and ADAPT studies consisted of an 18 month intervention with a 3 day per week exercise program for 1h, containing an aerobic phase, a strength phase, a second aerobic phase and a cool down phase. The pilot study of Messier et al., 2000 reported a warm-up phase and an intervention period of 6 months (65).

Two studies were categorized as other (1, 58). Aguiar et al., 2015 used an exercise protocol consisting of strength and flexibility training of the muscles (1). The exercises in

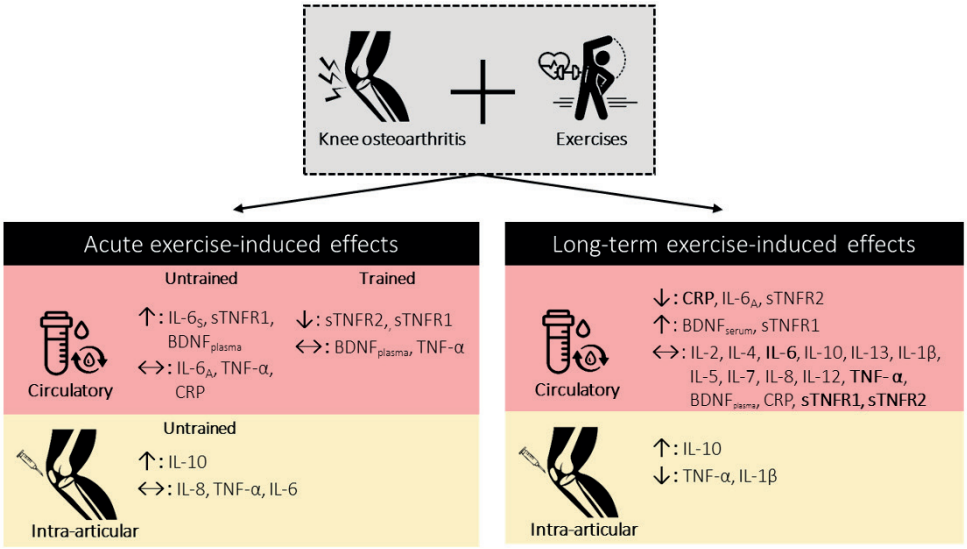

Figure 2. Summary of the main exercise-induced effects in KOA patients.
A division was made between acute and long-term exercise effects, and between circulatory (i.e. blood serum/plasma) and local (i.e. synovial fluid) levels.
'↑' indicates an increase , '↓' indicates a decrease, '↔' indicates no change, 'biomarkers written in **bold***' indicates evidence based on meta-analysis, 'biomarkers normally written' indicates evidence from individual studies.*
A: aerobics; S: strength training; IL: interleukin, sTNFR: soluble tumor necrosis factor receptor, BDNF: brain derived neurotrophic factor, TNF: tumor necrosis factor, CRP: C-reactive protein

the study of Liu et al., 2019, consisted of a warm-up phase, followed by either cycling (aerobics) or Tai Chi or Baduanjin, and ended with breathing techniques and a relaxation phase (58). Detailed information about the exercise protocols of each study is provided in Table 2.

The 18 investigated inflammatory markers were: IL1-β, IL-2, IL-4, IL-5, IL-6, IL-6sR, IL-7, IL-8, IL-10, IL-12, IL-13, TNF-α, soluble tumor necrosis factor receptor (sTNFR)-1, sTNFR-2, BDNF, CRP, CRPM and leptin. Seven studies reported results of biomarker analyses in peripheral blood plasma (3, 7, 32, 33, 66, 85, 86); nine in serum (1, 4, 29, 47, 58, 59, 67, 68, 80); in one study it was unclear whether the biomarkers were analyzed in serum or plasma (51); and four in dialysate of synovial fluid of the knee (38, 39, 65, 102). Four studies investigated the acute effects of exercise on inflammatory markers (29, 38, 39, 47), fifteen studies investigated the effects of exercise on basal levels (1, 3, 4, 7, 51, 58, 59, 65-68, 80, 85, 86, 102), and two studies investigated both the acute effect and the effect on basal levels (32, 33) (Figure 1b). Detailed information is available in Table 3.

Risk of bias within studies

Information regarding the quality assessment of the studies is provided in Table 4.

Randomized controlled trials

The quality of fifteen articles was determined with the ROB 2.0 tool (Table 4a). In eight included RCTs, there were "some concerns" in at least one risk of bias domain (3, 38, 58, 59, 65, 68, 85, 86). Seven RCTs had an overall "high ROB" because there were either "some concerns" for multiple domains or a "high ROB" in at least one domain (4, 7, 51, 66, 67, 80, 102) (Table 4a).

Only two RCTs provided detailed information on the randomization process (domain 1) (59, 68). In two RCTs, a "high ROB" arising from the randomization process (domain 1) was reported, as insufficient information about the allocation sequence concealment was available (7, 80). In two RCTs, the ROB due to deviations from the intended interventions (domain 2) was also "high" (7, 66) while most of the RCTs had a "low ROB" in this domain (3, 38, 58, 65, 68, 85, 86). In all RCTs (n=14), all outcome data were available for all randomized participants (domain 3), except for the study of Miller et al. (67). Apart from one study (51), all RCTs showed a "low ROB" regarding the measurements of the outcomes (domain 4).

Non-randomized or non-controlled trials

The quality of six articles was determined with the ROBINS-I tool (Table 4b). The NRCT of Germanou et al. and the NRUCT of Helmark et al., 2012 had both a "critical overall ROB" score on the ROBINS-I, because both articles had a critical ROB score in domain 5 (bias due to missing data) (29, 39). Four NRUCTs had a "serious overall ROB" score because there was a serious ROB score reported in at least one domain of the ROBINS-I (1, 32, 33, 47).

Exercise effects

Despite the association of inflammation with the pathogenesis of KOA, very few studies have investigated the impact of physical exercise on inflammatory mediators in patients with KOA. This section is further divided into two main parts: acute exercise effects and long-term exercise effects. Studies were allocated to the acute exercise effects section if changes in biomarker concentrations were captured during and immediately following a bout of exercise (i.e. < 24h after an acute bout of exercise). Studies were allocated to the long-term exercise effects section if changes in biomarker concentrations where captured > 24h post exercise (i.e. when the acute exercise effects were washed

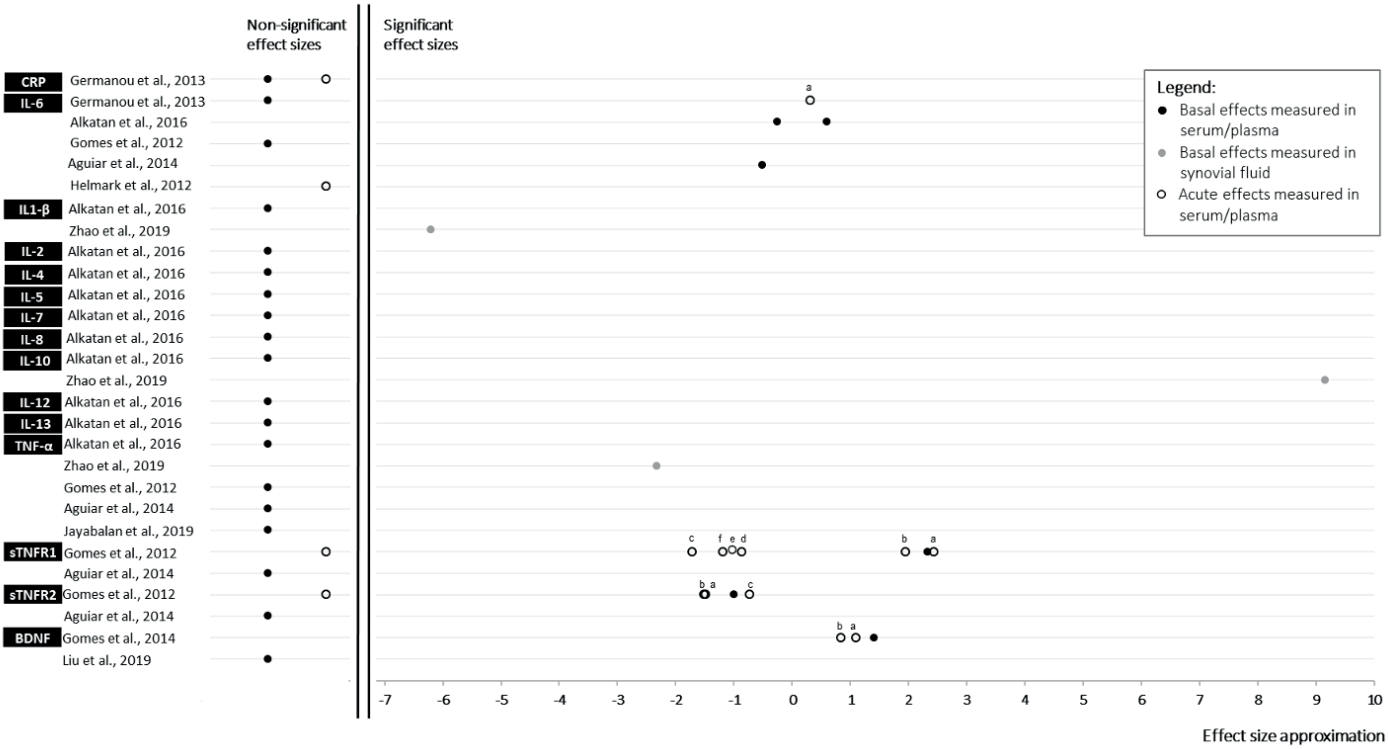

Figure 3. Impact of exercise therapy on different biomarkers in KOA patients (studies not incorporated into meta-analysis).
[a]: in untrained status pre vs. post exercise session. [b]: in untrained status pre vs. 30min post exercise session. [c]: in untrained status pre vs. 30min post exercise session. [d]: in trained status post vs. 30min post exercise session. [e]: post exercise session in untrained status vs. post exercise session in trained status. [f]: 30min post exercise session in untrained status vs. 30min post exercise session in trained status.

out). Detailed information of the individual study results can be found in Table 3 and a schematic overview of the main results is presented in Figure 2 and 3. Table 5 provides a summary of the exercise effects per biomarker. The biomarkers are referred as pro or anti-inflammatory based on their characteristics and context in which they were measured. Based on literature data, TNF-α, CRP, IL-1β (61, 96) can be considered as pro-inflammatory biomarkers, while IL-10, IL-4 and sTNFR1&2 as anti-inflammatory biomarkers (61, 87). IL-13 can also be considered as anti-inflammatory as it inhibits the expression of pro-inflammatory biomarkers (e.g. TNF-α, IL-8) (46). Depending on the context IL-6 can induce pro or anti-inflammatory effects and is therefore considered as a pleiotropic cytokine (17). When measured within 24 hours after an exercise session, circulating IL-6 is mainly secreted by the exercising muscles and has mainly anti-inflammatory properties. When measuring basal levels of IL-6, > 24 hours after an exercise session, circulating levels reflect rather pro-inflammatory status (17). Circulatory IL-5 is mainly released by a Th2 immune response to activate and recruit eosinophiles and basophiles (101). Leptin is also categorized as a biomarker with a pro-inflammatory character as it increases the expression of other pro-inflammatory cytokines in the circulation (e.g. TNF-α, IL-6) (44). Chemokines like circulatory IL-8 are pro-inflammatory because of the attraction of immune cells to the inflammation site and IL-8 induces matrix metalloproteinase (MMP) activity (12). IL-8 is also involved in increased capillarization response following exercise and might therefore also reflect beneficial signaling (26) Intra-articularly, macrophages secrete pro-inflammatory cytokines like IL-12 to initiate a Th1 response (16). Also intra-articular IL-7 is considered as a pro-inflammatory cytokine in OA. It is secreted by chondrocytes and induces cartilage destruction. Furthermore, it may initiate a T-cell driven immune response (95).

Acute exercise effects

Effects measured in serum or plasma

The circulatory blood concentrations of the pro-inflammatory biomarkers CRP (ES: 0.052) (29) and TNF-α (ES: -0.019; ES: 0.081) (32, 47) in patients with KOA did not change after a single bout of exercise. Only after a single bout of strength training, an increase in IL-6 concentration was demonstrated (ES: 0.314) (29), as IL-6 did not change after an acute session of aerobic training (32). Furthermore, the sTNFR1 (ES: 2.444) (32) and BDNF (ES: 1.101) (33) levels were increased immediately after one aerobic session in untrained condition, while a decrease was noticed for sTNFR2 (ES: -1.483) (32). In trained condition (following a 12 week aerobic training program), both sTNFR1 (ES: -1.714) and sTNFR2 (ES: -0.727) levels significantly decreased 30 minutes after an acute exercise session, while an acute training session in trained condition had no significant effect on BDNF (33).

In summary, an acute exercise session elicited an acute myokine response (ES IL-6: 0.314), as well as a decrease in sTNFR2 (ES: -1.483) and increase in BDNF (ES: 1.101) in untrained condition. Myokine response seems more pronounced in strength training compared to aerobic training, as well as in trained condition (ES sTNFR1: -1.714; ES sTNFR2:-0.727). No evidence was found for an acute pro-inflammatory effect (ES CRP: 0.052 and ES TNF-α: -0.019 and 0.081) following an acute bout of training.

Effects measured in synovial fluid

No difference in the levels of intra-articular inflammatory biomarkers (TNF-α, IL-8, IL-6 and IL-10) was found following exercise versus control. Due to the invasive repetitive sampling procedure (6 samples between 1 and 3 hours following exercise or control), the inflammatory biomarkers increased

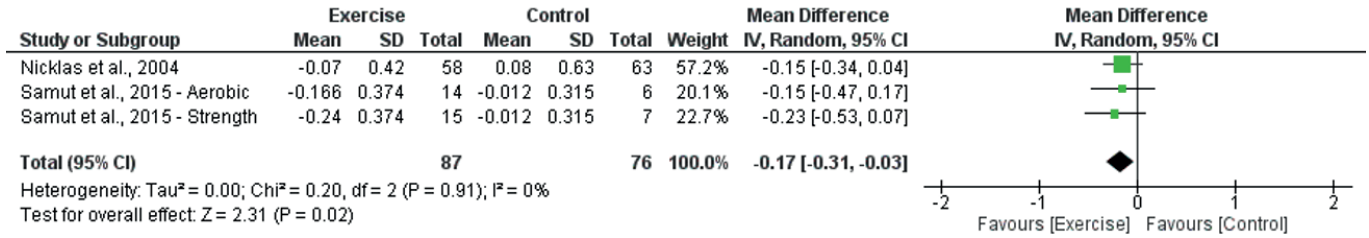

Figure 4. Forestplot of comparison exercise vs. control for basal CRP levels.

similarly in both groups, except for IL-10. This anti-inflammatory biomarker did only increase after the exercise condition. In another study, intra-articular IL-6 levels, measured 10-15 minutes after a strength exercise showed a tendency to increase (ES=0.900), but this effect was not statistically significant.

In summary, a single bout of exercise elicited an intra-articular anti-inflammatory response as IL-10 increased. No evidence for an acute exercise induced intra-articular inflammatory response was demonstrated.

Long-term exercise effects

Effects on pro-inflammatory markers measured in serum or plasma

For three pro-inflammatory markers in the blood (i.e. CRP, IL-6 and TNF-α), a meta-analysis was performed (Figure 4 -6) by combining results of two studies (68, 80). Basal CRP levels decreased (mean difference: -0.17, 95% CI -0.31 to -0.03; p=0.02; I^2=0%; p= 0.91) while IL-6 (mean difference: 0.21, 95% CI -0.44 to 0.85, p= 0.52; I^2=61%, p=0.08) and TNF-α concentrations (mean difference: -0.57, 95% CI -1.47 to 0.32, p=0.21; I^2=71%, p=0.03) did not change in KOA patients after an intervention period ranging from 6 to 18 weeks in comparison to the control group. Those studies that could not be included in the meta-analysis showed that, an exercise program of either cycling (ES: -0.259), swimming (ES: -0.596), or flexibility training in combination with strength exercises (ES: -0.513) induced a significant decrease in circulatory levels of IL-6 (1, 3). Additionally, swimming or cycling for 6 weeks did not impact other pro-inflammatory cytokines in the blood circulation of KOA patients (i.e. IL-1β, IL-5, IL-7, IL-8, IL-12, TNF-α) (3). On the other hand, no changes in IL-6 (SMD: log (IL-6): -0.02 [95%CI: -0.32 to 0.28]), TNF-α (SMD: log(TNF-α): 0.10 [95%CI: -0.07 to 0.26]) and CRP (SMD: log(CRP): -0.25 [95% CI: -0.69 to 0.20]) were demonstrated when KOA patients performing strength exercises for 4-6 weeks were compared with a true KOA control group (51). As well, a single bout of strength training had no influence on the basal IL-6 (ES: 0.035) and CRP (ES: 0.039) levels when measured 24h after the exercise (29). Furthermore, no significant changes in IL-6 (ES:-0.278) and TNF-α (ES: 0.546) were observed when KOA patients performed aerobic training for 12 weeks (32), neither TNF-α (ES: 0.080) was significantly influenced after flexibility training in combination with strength exercises (1), and IL-1β was also not significantly changed in patients with KOA who underwent a strength intervention (ES: 0.146) (4).

Effects on anti-inflammatory markers measured in serum or plasma

Besides pro-inflammatory markers, anti-inflammatory cytokines (IL-2, IL-4, IL-10, IL-13, sTNFR1, sTNFR2) were also investigated in blood serum or plasma of patients with KOA (3, 68, 85). The results of two studies (68, 85) were combined into a meta-analysis for sTNFR1 and sTNFR2 (Figure 7-8). No significant changes in basal sTNFR1 (mean difference: -34.94, 95% CI -125.60 to 55.72, p=0.45, Figure 7) and sTNFR2 (mean difference: -214.27, 95% CI -769.99 to 341.15, p= 0.46, Figure 8) levels were found in KOA patients after an intervention period ranging from 12 weeks to 18 months in comparison to the control group. However, after a 12 week aerobic intervention in woman with KOA, sTNFR1 (ES: 2.325) was increased while sTNFR2 (ES: -0.997) was significantly decreased (32). Other anti-inflammatory markers (i.e. IL-2, IL-4, IL-10, IL-13) did not significantly change in patients with KOA after an intervention period of either swimming or cycling (3).

Effects on BDNF measured in serum or plasma

Results of basal BDNF were available in two studies (33, 58). No significant changes in serum BDNF levels were noticed after 12 weeks when comparing the three intervention groups, namely Tai Chi (ES: -0.370), Baduanjin (ES: -0.512), aerobics (ES: -0.185), with the control group (58). On the other hand, an increase in plasma BDNF (ES: 1.412) was demonstrated in female participants with KOA who performed a walk training of 12 weeks (33).

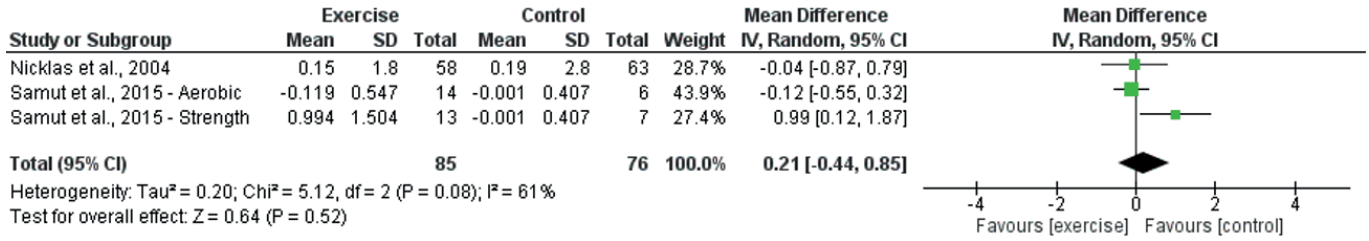

Figure 5. Forestplot of comparison exercise vs. control for basal IL-6 levels.

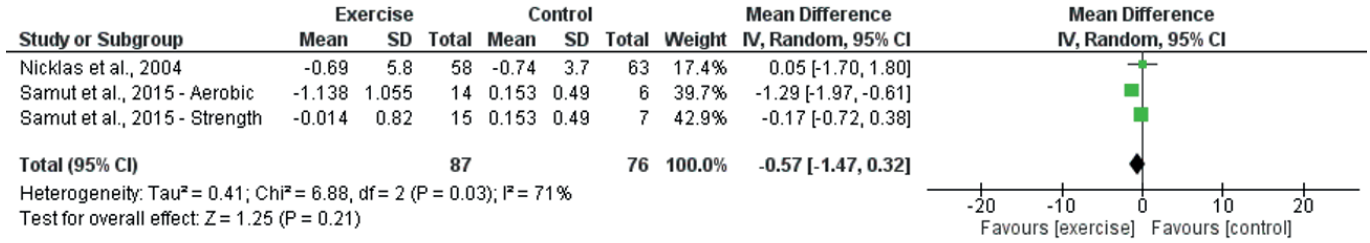

Figure 6. Forestplot of comparison exercise vs. control for basal TNF-α levels.

In summary, our meta-analysis showed that basal CRP can be reduced in patients with KOA through an exercise intervention of 6-18 weeks, while IL-6 and TNF-α levels did not significantly change. Also, sTNFR1/2 did not significantly change after at least 12 weeks exercising. The exercise-effect on different other biomarkers was less clear and, unfortunately, there were insufficient data available to perform a meta-analysis. Nevertheless, a low degree of evidence was present for a decrease in IL-6 after swimming (ES: -0.596), cycling (ES: -0.259) or flexibility training in combination with strength exercises (ES: -0.513) for 12 weeks, increase in sTNFR1 (ES: 2.325), decrease in sTNFR2 (ES: -0.997) and increase in plasma BDNF (ES: 1.412) after 12 weeks of walking.

Effects measured in synovial

Intra-articular, strength training of 12 months decreased basal levels of TNF-α (ES: -2.322) and IL-1β (ES: -6.199), and increased the levels of anti-inflammatory cytokine IL-10 (ES: 9.163) (102). Additionally, a combined exercise and diet program of 6 months decreased the IL-1β synovial fluid levels significantly (65).

In summary, we found evidence that a strength intervention with static low angle squats can significantly counteract local inflammation in the knee reflected by increased intra-articular levels of IL-10 (ES: 9.163), and reduced IL-1β (ES: -6.199) and TNF-α (ES: -2.322).

DISCUSSION

This systematic review provides an overview of studies investigating exercise-induced effects on inflammatory markers and BDNF in patients with KOA, with a focus on both acute and basal circulatory and/or intra-articular effects. Overall, our literature study provides some evidence that exercise therapy in patients with KOA can elicit circulatory and intra-articular anti-inflammatory effects, on the long-term as well as after a single exercise session. Twenty-one articles were included (acute: n=4; basal: n=15; both: n=2) that reported on eighteen different inflammatory markers and BDNF. For five biomarkers (CRP, TNF-α, IL-6, sTNFR1 and sTNFR2) a meta-analysis was performed, to investigate the long-term exercise induced effects. Due to limited available data of the other biomarkers, no meta-analysis could be performed but effect sizes were estimated (where possible).

CRP is an important biomarker that reflects circulatory inflammation as it is produced, after induction (primarily) by IL-6, in the acute phase of the inflammatory process in the liver (96). CRP concentrations did decrease after a chronic exercise intervention program in KOA patients compared to control patients with KOA which did not perform exercises (MD: -0.17; 95% CI: -0.31 to -0.03) (Figure 4), while one single bout of exercise did not change basal and acute CRP levels (29). These findings suggest that one single bout of exercise is not effective to decrease basal CRP concentrations in patients with KOA, but it seems effective to reduce resting blood CRP concentrations after maintaining exercise therapy, leading to an anti-inflammatory effect on the longer term. These results are in line with two recent meta-analyses which reported a significant reduction in basal CRP levels after an aerobic or strength training exercise intervention in older adults (81, 103).

Because basal levels of CRP decreased, we expected that IL-6 levels would also decrease in patients with KOA in response to exercise therapy, though this was not confirmed by our meta-analysis (Figure 5). One of the studies incorporated in the meta-analysis (80) reported that the sample size of their study was too small (n=42) and the intervention period of 6 weeks was too short to demonstrate significant changes in the investigated inflammatory markers (80). Two other included articles in this review, with a pre-experimental study design (without control group), reported a decrease in circulatory IL-6 levels (1, 3). Noticeably, the intervention period of both studies was twice as long as the study of Samut et al. (80). Accordingly, it seems that an exercise therapy program of at least 12 weeks is necessary to achieve such an anti-inflammatory response on the long-term; however, this needs confirmation by high-quality RCT's.

Effects of an exercise intervention can interact with

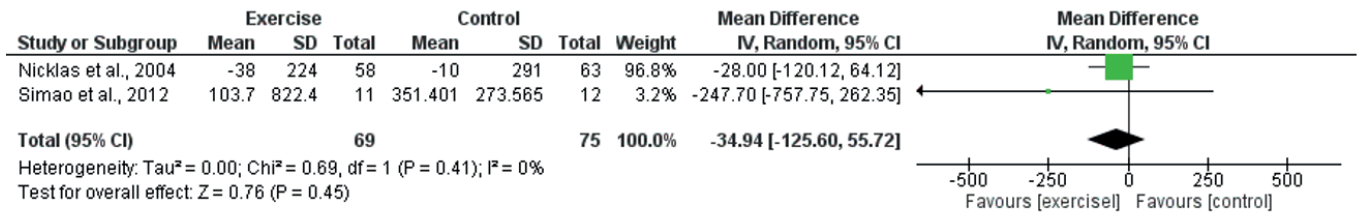

Figure 7. Forestplot of comparison exercise vs. control for basal sTNFR1 levels.

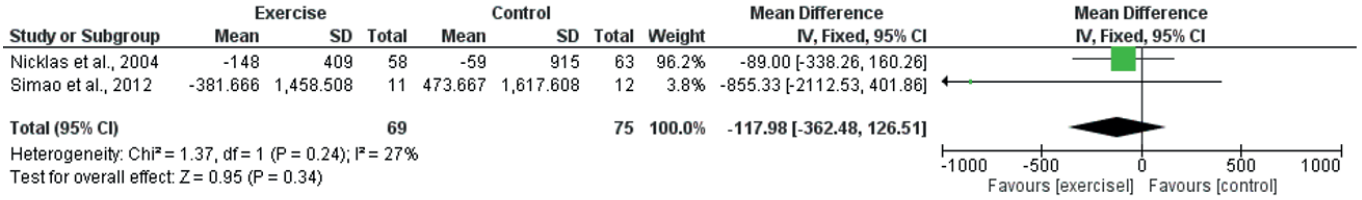

Figure 8. Forestplot of comparison exercise vs. control for basal sTNFR2 levels.

changes in fat and body composition. Germanou et al. (29) observed significantly higher resting IL-6 levels in participants with KOA at baseline in contrast to control participants with healthy knees. This study included only obese female participants with KOA (29). To explain the higher resting levels in OA patients, the link between obesity and inflammation should be considered. White adipose tissue can function as a key endocrine organ by releasing multiple pro-inflammatory adipokines (leptin, chemerin, visfatin etc.) and cytokines (IL-6, TNF-α, etc.) and may contribute, mediate or interact with the inflammatory process (27, 50, 83). At the level of the knee joint, the infrapatellar fat pad also produces locally cytokines (e.g. IL-6, IL-8, TNF-α) and adipokines (e.g. visfatin, adiponectin, adipsin), and stimulates the progression and development of synovitis that contributes to the pathophysiological changes in the KOA process (48). Certainly, obesity is one of the risk factors for OA because of the associated local effects (i.e. higher joint loading) and systemic effects (i.e. inflammation) (76). Almost half of the included studies in this review were patients with obesity. We also included studies that investigated the additional effect of a diet intervention besides an exercise intervention in patients with KOA. However, we focused only on the results of the exercise intervention in this systematic review. Those studies showed that a diet program was more effective to reduce resting leptin (67), IL-6 (66, 68), sTNFR1 (68), CRP (7, 68) levels than exercise therapy. In this respect, it should be noted that interventions focusing solely on weight loss as a treatment for OA may negatively impact muscle mass and strength, and consequently, mobility (11). Accordingly, it is important to propose a weight loss program in combination with exercise therapy for overweight or obese patients with OA; which is also stated in the American College of Rheumatology guidelines (11).

Sex is also an important risk factor for KOA, besides obesity. In general, the prevalence of KOA is 21.7% in women and only 11.9% in men (19). These percentages can explain why the studies in our systematic review mainly included female participants (i.e. about 80%). In general, male KOA study participants were strongly underrepresented (only 20%) in the included articles. In six articles (4, 29, 32, 33, 38, 86), the study participants even consisted only of females. It is known that females experience OA in a different way than males. For example, females suffer from a higher degree of KOA symptomatology, which is reflected in higher levels of disability and pain (35). KOA can have a multifactorial origin, but hormonal changes, previous knee injury and anatomy of the knee are the most important ones (35). Especially during the menopause, females experience a decrease in oestrogen. In fact, oestrogen has protective properties on the cartilage, and these protective properties seem to decline in the post-menopausal period (35). Strikingly, none of the included studies compared neither baseline nor exercise-induced changes in inflammatory biomarkers between male and female participants. Therefore, it remains unclear what the influence of sex can be on the expression of certain inflammation related biomarkers after exercise therapy. This shortcoming needs to be addressed in future trials to further clarify possible differences between males and females, as suggested by Hame and colleagues (35).

Another pro-inflammatory cytokine of interest was TNF-α and its soluble receptors; sTNFR1 and sTNFR2. TNF-α is one of the key cytokines involved in the initiation of the immune response. The soluble TNFRs function as inhibitors of TNF-α as they can compete with TNF-α for binding to the cell surface TNFRs (85, 98). According to Simao et al., a reduction in sTNFR1 and sTNFR2 levels may reflect anti-inflammation and reduces the inflammatory process (85). In this systematic review, our meta-analysis (Figure 7-8) demonstrated that there were no significant reductions in basal levels of sTNFR1 and sTNFR2 after exercise therapy in patients with KOA. However, for both receptors, a trend to decrease in mean difference was observed in favor of the exercise therapy groups but this decrease was not statistically significant. Furthermore, the studies that investigated the exercise-induced effects on basal TNF-α levels did not observe a significant change after the intervention (1, 3, 32, 51, 68, 80). This finding is in line with results of studies that investigated the effect of exercise in populations without OA. For example, evidence of a large-scale study in a non-disabled elderly population at risk for physical disability showed that a 12-month exercise intervention did not result in significant changes of circulatory TNF-α; however, they did observe a significant decrease in sTNFR1 and IL-6, but not in sTNFR2 (8). It is important to highlight that capturing blood concentrations of TNF-α using immunoassays is not evident since this cytokine has a short half-life of 4.6 min. Circulatory sTNFR1 and sTNFR2 are more stable and can therefore provide an indication of the active TNF-α signaling during inflammatory conditions (85, 88).

The neurotrophin BDNF was investigated in two studies with contradictory results (33, 58). Liu et al. (58) measured serum BDNF while Gomes et al. (33) measured plasma BDNF. Plasma levels of BDNF reflect the free active circulatory BDNF while serum BDNF indicates the total BDNF concentration (i.e. it is the sum of stored BDNF within the platelets + plasma BDNF) (97). As such, serum BDNF can show variations in BDNF levels over a longer time whereas plasma BDNF gives temporary concentrations. Moreover, it is more appropriate to measure BDNF in blood serum instead of plasma because plasma BDNF levels are unstable (≤ 1 hour present) (75, 84). Measurement of plasma BDNF can also be affected by sample handling as BDNF can be released from platelets, that are present in the blood tube, when activated (75). Based on this knowledge, we agree that the determination of serum BDNF is more correct to show long-term exercise induced effects in patients with KOA. Accordingly, no

significant changes in serum BDNF were observed in patients with KOA after 12 weeks of Tai Chi, Baduanjin or cycling (58). This result is in contrast with others as they found an increase in BDNF in healthy elderly after exercise therapy (15, 18). However, circulatory BDNF in OA is increased as compared to healthy controls (70). These elevated levels of BDNF can play a role in central sensitization, (70) which is present in some patients with KOA and can be an explanation for chronic pain complaints (69, 70).

Besides long-term circulatory effects of exercise therapy, local effects in the knee were investigated by Zhao et al. which determined synovial fluid levels (102). Their results were promising as static low angle squats were effective to reduce local inflammation (i.e. synovitis) in the knee joint space of people with KOA. Messier et al. did not report on the IL1-β levels of the exercise group alone, but they demonstrated a decrease in synovial fluid levels of IL-1β in eight patients with KOA that followed a weight loss program in combination with exercise therapy (65). To our knowledge, no similar clinical research on long- term effects in humans is present in the literature, but the results are also comparable with pre-clinical research. During exercise, repeated mechanical loading is provoked within the knee. In-vitro studies demonstrated that IL-1β induced biomarkers are downregulated when chondrocytes are mechanically stimulated. Furthermore, inflammatory responses related to IL-1β and TNF-α are counteracted upon chondrocyte stimulation (56). In-vivo, it was shown that IL-10 was synthesized in menisci of rabbit knees when passive motion therapy was applied (56). Further research on the long-term effects of exercise therapy in patients with KOA and healthy individuals is necessary to further elucidate the immune response at the local level of the knee.

Little is known about how exercise-induced effects on inflammation related biomarkers in the synovial fluid are related to circulatory biomarkers in patients with KOA, and vice-versa. On the one hand, it is unclear to which extent exercise-induced changes in systemic inflammation contributes to or reflects changes in intra-articular inflammatory processes in patients with KOA. On the other hand, in previous research (9), different hypotheses on the working mechanism of exercise therapy in KOA patients are suggested. One of the hypotheses proposed that exercise therapy improves the blood circulation and allows the synovial fluid to move, causing an outflow of inflammation related markers from the joint cavity (9). Unfortunately, there is a lack of data available and future research is needed to confirm these hypotheses. In this systematic review, we did not identify articles investigating both systemic and intra-articular effects on inflammation related biomarkers. The study of Helmark et al. (39) already initiated this investigation as cartilage oligomeric protein (COMP) was determined in both serum and synovial fluid. However, for inflammatory related biomarkers like IL-6, the determinations were only performed in synovial fluid (39). In general, studies investigating biomarker levels in synovial fluid are very challenging as intra-articular fluid is very limited (49). On the other hand, our systematic review was able to provide an overview of inflammation related biomarkers in the synovial fluid and provides important new insights to the research community.

A distinction between acute exercise-induced effects and long-term effects was made because certain cytokines, especially pleiotropic cytokine IL-6, have properties that differ from an acute or basal setting. Acute circulatory levels of IL-6 can have anti-inflammatory effects, while elevated resting levels rather reflect a pro-inflammatory status. Elevated blood levels of IL-6 immediately after exercising are mostly derived from contracting skeletal muscles. This myokine release is dose-dependent with a higher release seen after more intensive and/or longer muscle activity (22). This relationship can also be substantiated to the KOA population as only after an acute bout of strength training, a significant increase in IL-6 was observed in patients with KOA, but this effect washed-out after 24 hours (29). Furthermore, a decrease in acute levels of sTNFR1 and sTNFR2 was observed in trained condition, while this was only the case for sTNFR2 in untrained condition (32). Indeed, IL-6 induces sTNFRs release and regulates the TNF-α levels (74). However, for BDNF an increase was only observed in untrained status (33). Nevertheless, this finding is based on one study, therefore future investigations are needed. No indications for exacerbation of inflammation were found after an acute bout of exercise, as circulatory CRP and TNF-α levels did not change. Only six articles investigated the acute exercise-induced effects. Literature regarding acute effects on circulating anti-inflammatory cytokines such as IL-10 and IL-1RA is lacking. However, intra-articularly, IL-10 did significantly increase after a single bout of exercise (38). A small pilot-study in which five healthy young men performed a single running session of 30 minutes also suggested that an acute bout of running can decrease intra-articular inflammation (43). However, to our knowledge, this is the only clinical study available in literature that investigated a wide set of biomarkers in synovial fluid in healthy individuals who performed an acute exercise session. Studies with a larger sample size are recommended to investigate the acute intra-articular response on exercise.

The findings of this systematic review imply that exercise therapy for people with KOA can trigger anti-inflammatory reactions, making this intervention effective and accessible to control the inflammation (i.e. synovitis and CLIP) associated with KOA. However, a proportion of the patients with KOA still believe that exercise therapy or physical activity is dangerous and will cause harm (89). To overcome such incorrect beliefs, pain science education can be an added value (89), and the findings of the present review and meta-analysis suggests that such pain science education for patients with KOA should be updated with information about the anti-inflammatory properties of exercise therapy. A large RCT in which people with OA of the lower extremities (i.e. knee, hip, lower back, ankle, feet OA) performed strength training for 8 weeks in combination with 30 minutes education sessions (in which the management of barriers to exercise and strategies to exercise safely within OA are covered) showed a significant decrease in serum TNF-α post intervention (62). Furthermore, a recent systematic review of RCTs concluded that exercise is safe for patients with KOA (14).

Here, we summarize the strengths of this systematic review. First, we reported the findings according to the PRISMA guidelines. Second, multiple independent blinded researchers performed the study selection and quality assessments. For the study selection, a predefined set of in and exclusion criteria were determined and this protocol was published on PROSPERO (CRD42020162746) prior to final database search, study inclusion and data extraction. Regardless of the author details

of the papers (e.g. name and/or institution), the quality of the studies was rated. As such, author details had no influence on the results of the systematic review. Furthermore, the quality assessments for the RCTs were performed using the most recently developed ROB 2.0 tool (91). Third, a meta-analysis of five different biomarkers of interest was performed. Effect sizes of results that could not be incorporated into a meta-analysis were estimated where possible, allowing easier comparison of the results of those studies. Finally, this is the first systematic review that provides a comprehensive overview of acute and basal exercise-induced effects on inflammatory biomarkers in KOA patients (measured in serum, plasma or synovial fluid). The systematic review of Bricca et al., does not include acute exercise- induced effects and it seems that they made no distinction between systemic and intra-articular effects (14). Furthermore, these authors only focused on one type of study design, RCTs (14). To distinguish systemic from local effects, it is essential to measure biomarkers respectively serologically or intra-articularly. Levels of systemic markers result from multiple tissues or joints throughout the body, whereas synovial fluid focusses only on the state of one joint (20). In fact, the (anti)inflammatory response to exercise may differ in the peripheral circulation compared to the synovial fluid.

This systematic review has also some limitations. First, the included studies reported on different cytokines. Therefore, it was not possible to perform a meta-analysis for every biomarker studied. Furthermore, a low number of studies reported on acute exercise effects. Additionally, included studies reported their results in various ways (e.g. only graphs, narrative descriptions, or quantitative descriptions). When quantitative data were not reported and authors did not respond to our request for these data, we performed additional analyses in order to obtain the best possible estimates. Graphs were analyzed with GetDataDigitizer as accurate as possible to obtain an estimate of the effects. Furthermore, to perform a meta-analysis, mean values were required. With the use of mathematical formulas (40, 99), mean values were approximated if they were not available. However, these method comprises risks for errors. Third, the study designs of the included studies were heterogeneous. More high qualitative studies, preferably RCTs that investigate both acute and basal exercise-induced effects on a wide set of inflammatory markers and BDNF, are needed to overcome this limitation and further extrapolate potential underlying relationships between acute and basal exercise-induced effects. To investigate the differences between different types of exercise therapy (i.e. strength, aerobics, flexibility training etc.), interventional studies that determine the same set of biomarkers and BDNF serologically and intra-articular are needed in people with OA. As such, it can be demonstrated whether there is a difference in inflammatory response between those types of exercise therapy because there was lack of data on this topic. Finally, per definition, reviews are limited by the quality of the available research reports. Unfortunately, sleep is not considered as a potential confounder of studies examining the exercise effects on inflammation in patients with KOA. This is a shortcoming that needs to be addressed in future work. Indeed, insomnia is a severe and very common comorbidity in patients with KOA (2, 92, 100), and it has a dysregulating role on inflammatory pathways in the general population as well as in KOA patients, with increases in markers of systemic inflammation such as IL-6 and CRP (23, 37, 45).

CONCLUSION

In general, this systematic review provides some evidence that exercise therapy is effective to induce an immunomodulatory response in KOA patients characterized by mainly increased anti-inflammatory signaling and decreased pro-inflammatory signaling. Evidence for both acute and basal exercise effects was found, however it seemed that this effect was more pronounced in trained versus untrained status. Both intra-articular and systemic inflammation was downregulated by exercise therapy. Furthermore, exercise therapy can be considered as safe for the KOA population because no exacerbation of inflammation was observed.

ACKNOWLEDGEMENTS

The authors declare no conflicts of interest.

SUPPLEMENTARY TABLES

Supplementary material (supplementary tables 1 and 2) can be obtained upon request by contacting the corresponding author via ivan.bautmans@vub.be.

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Table 1:
Search terms PICO

	P (Osteoarthritis)	I (Physical Exercise)	C	O (inflammatory markers & BDNF)
PubMed	"Osteoarthritis"[Mesh] osteoarthr*	"Exercise"[Mesh] "Exercise Movement Techniques"[Mesh] "Exercise Therapy"[Mesh] "Resistance Training"[Mesh] "Sports"[Mesh] strength training aerobic training exercise		"Inflammation"[Mesh] "Acute-Phase Proteins"[Mesh] "Interleukins"[Mesh] "Cytokines"[Mesh] "Brain-Derived Neurotrophic Factor"[Mesh] inflammation acute phase reaction interleukin cytokine brain derived neurotrophic factor BDNF
WOS	osteoarthritis osteoarthr*	Exercise Exercise Movement Techniques Exercise Therapy Resistance Training Sports strength training aerobic training		Brain-Derived Neurotrophic Factor Inflammation Acute-Phase Proteins Interleukins Cytokines BDNF brain derived neurotrophic factor inflammation acute phase reaction interleukin cytokine
PEDro	osteoarthr*	exercis* physical* training therapy		inflam* tumor necrosis factor* cytokin* interleukin* “brain derived neurotrophic factor” BDNF

No filters were used in PubMed. In Web of Science ‘Basic Search/Topic/All years’ was chosen. In PEDro we chose for ‘Method: Clinical Trial’ on the ‘Advanced Search’ page. Only search terms in the ‘Abstract & Title’ box were filled in and matched with ‘AND’.

Table 2:
Exercise protocols

Reference	Inter-vention Period	Frequency	Duration	Intensity/load	Exercise modality
Aerobic (A) & Strength (S)					
Beavers et al., 2014[1]	**18 mo**	**3x/wk**	**1h** 2x 15' 20' 10'	 50-75% HRR 1-2x10-12 reps; 1'-1.5' rest interval NA	 exercise: A: walking (before and after strength) S: leg ext., leg pr., seated: leg curl & calf raise, row, vertical chest or incline press cool down
Loeser et al., 2017	**18mo**	**3x/wk**	**1h** 2x 15' 20' 10'	 50-75% HRR 1-2x10-12 reps; 1'-1.5' rest interval NA	 Exercise: A: walking (before and after strength) S: leg ext., leg pr., seated: leg curl & calf raise, row, vertical chest or incline press Cool down
Messier et al., 2000	**6 mo**	**3x/wk**	**1h** 5' 2x 10' 20'-30' 5''	 N/A 50-75% HRR 10-12 reps; 1'-1.5' rest interval NA	 warm up exercise: A: walking (before and after strength) S: leg ext., toe raise, leg curl, military press, upright row, chest fly, pelvic tilt (upper body: dumbbells; lower body: cuff weights) cool down
Messier et al., 2013[1]	**18 mo**	**3x/wk**	**1h** 2x 15' 20' 10'	 50-75% HRR 1-2x10-12 reps; 1'-1.5' rest interval NA	 exercise: A: walking (before and after strength) S: leg ext., leg pr., seated: leg curl & calf raise, row, vertical chest or incline press cool down
Miller et al., 2004	**18mo**	**3x/wk**	**1h** 2x15' 15' 15'	 50-75% HRR 2x12 reps; 1'-1.5' rest interval (Weight progressive ↑) NA	 Exercise: A: walking (before and after strength) S: leg extension, leg curl, heel raise, step-up (ankle cuff weights, weighted vest) Cool down
Nicklas et al., 2004[2]	**18 mo**	**3x/wk**	**1h** 2x 15' 15' 15'	 50-75% HRR 2x12 reps; 1'-1.5' rest interval (Weight progressive ↑) NA	 exercise: A: walking S: leg extension, leg curl, heel raise, step-up (ankle cuff weights, weighted vest) cool down
Other					
Aguiar et al., 2014	**12 wks**	**3x/wk**	**80'** 3x30" NA NA	 NA 3x10 reps (wk 1-2), 3x15 reps (wk 3-4); 60% MF 3x10 reps (wk 5-6), 3x15 reps (wk 7-8); 70% MF 3x10 reps (wk 9-10), 3x15 reps (wk 11-12); 80% MF 60" rest interval same progression in sets and reps as OKC-ex same progression in sets and reps as OKC-ex	 exercise: F: passive stretching: Iliopsoas, rectus femoris, iliotibial band active stretching: Hamstrings, Gastrocnemius, hip adductors S: Hamstrings, Quadriceps, Glut max, Glut med, Abdominals Open kinematic chain (OKC)-exercises with leg weights squat exercises (45° knee flexion) Abdominals: isometric (wk 1-4); concentric (wk 5-12)
Liu et al., 2019	**12wks**	**5x/wk**	**1h** 10' 30' 10' 10'	 70-75% HRmax 	Exercises: Warm-up Cycling (A) or Tai Chi or Baduanjin Breathing techniques Relaxation
Aerobic (A)					
Alkatan et al., 2016	**12wks**	**3x/wk**	**Progressive ↑** From 20-30' to 40-50'	**Progressive ↑** 40-50% HRR 60-70% HRR	Exercises: cycling (A) or swimming (A)
Gomes et al., 2012	**12 wks**	**3x/wk**	**Progressive↑** 5' 30' (+5' /2 wks) 5'	**Progressive ↑** NA HRmax: 70% (wk 1-3); 75% (wk 4-7); 80% (wk 8-12) NA	**TRAINING (T)** warm up: walking exercise: walking cool down: walking
		1x Pre T, 1xPost T	**50'** 2' 18' 30'	 1mph (0% inclination) 2 mph (0% incliniation)	**ACUTE BOUT** warm up: walking treadmill exercise: walking treadmill cool down: lie down
Gomes et al., 2014	**12 wks**	**3x/wk**	**Progressive↑** 5' 30' (+5' /2 wks) 5'	**Progressive ↑** NA HRmax: 70% (wk 1-3); 75% (wk 4-7); 80% (wk 8-12) NA	**TRAINING(T)** warm up: walking (land + aquatic) exercise: walking (land + aquatic) cool down: walking (land + aquatic)
		1x Pre T, 1xPost T	**50'** 2' 18' 30'	 1mph (0% inclination) 2 mph (0% incliniation)	**ACUTE BOUT** warm up: walking treadmill exercise: walking treadmill cool down: lie down
Jayabalan et al., 2019	**45' x2**	**1x pre T, after 15', 30' and 45'**	**45'**	40-60% HRR 1.3m/s	**ACUTE BOUT** 1x45': continuous walking on treadmill 1x45': interval walking on treadmill
Samut et al., 2015	**6 wks**	**3x/wk**	**Progressive↑** 5' wk1: 15' (+5'/wk)[3] 5'	**Progressive ↑** <60% HRmax[3][4] HRmax[4]: 65-70% (wk 1-4); 70-75% (wk 5-6) NA	 warm-up: walking on treadmill exercise: walking on treadmill cool down: walking on treadmill[3]
Strength (S)					
Armagan et al., 2012	**6mo**	**1x/day**	**NA**	2 sets of 20 reps; 2' break between the sets	Quadriceps isometric and isotonic strengthening, joint range of motion, and hamstring stretching exercises

Germanou et al., 2013	24h		NA		
		1xPre,1x post, 1x24hpost		1x5 reps; maximal; (30" rest interval); at random: 90°/s, 120°/s, 150°/s	test: isokinetic (dynamometry chair): concentric knee ext/flex; affected leg:
		1x		6x10 reps; maximal; (30" rest interval); 90°/s (set 1+6); 120°/s (set 2+5); 150°/s (set 3+4)	exercise: isokinetic (dynamometry chair): concentric knee ext/flex; affected leg
Helmark et al., 2010	**1 day**	**1 session**	**±1h**		
			5'	NA	warm up: bicycle
			NA		5-7 RM test: leg press; one leg (start at 90° knee flex)
			NA	25x10 reps; 1.5' rest interval; 60% 1RM [5]	exercise:leg press; one leg (start at 90° knee flex)
Helmark et al., 2012	**1 day**	**1 session**			
			5'	NA	exercise: warm up: bicycle
			NA	10x8 reps; 2.5' rest interval; 60% 1RM [6]	leg press (knee extension); one leg (start at 90° knee flex)
Kim et al., 2021	**4-6wks**	**3x/wk**	**60'**	**Progressive ↑**(with ankle cuffs)	Aquatic exercises
			10'		Warm-up
			20'		Flexibility and strength
			20'		Low intensity endurance: e.g. walking
			10'		Cool down
Samut et al., 2015	**6 wks**	**3x/wk**	NA	**Progressive ↑**	
			5'	<60% HRmax[3][4]	warm-up: walking on treadmill
			NA	session 1: 1x5 reps (60°/s, 90°/s, 120°/s, 180°/s), + 1 set each following session until 6 sets (20" rest interval between sets, 2' rest between legs)	exercise: isokinetic (dynamometry chair): concentric knee ext/flex, both legs (ROM knee adjusted between 10°-80°)
			5'	NA	cool down: walking on treadmill[3]
Simão et al., 2012	**12 wks**	**3x/wk**			
					SQUAT-group:
			10'	HRmax: 70%	warm up: bicycle
			NA	3" 10° knee flex /3" 60° knee flex progressive ↑ volume (time↑/ # sets↑, rest time↓)	exercise: SQUAT (isometric) start 10° knee flex/end 60° knee flex
					PLATFORM-group
			10'	HRmax: 70%	warm up: bicycle
			NA	3" 10° knee flex /3" 60° knee flex progressive ↑ volume (time↑/ # sets↑, rest time↓, vibratory frequency 35-40Hz; amplitude 4; acceleration 2.78-3.26g)	exercise: SQUAT on WHOLE BODY VIBRATION PLATFORM (isometric): start 10° knee flex/end 60° knee flex
Simão et al., 2019	**12wks**	**3x/wk**	10'	HRmax: 70%	SQUAT-group:
			NA	3" 10° knee flex /3" 60° knee flex progressive ↑ volume (time↑/ # sets↑, rest time↓)	warm up: bicycle exercise: SQUAT (isometric) start 10° knee flex/end 60° knee flex
Zhao et al., 2019	**2y**	**2x/day**	30'	NA	Exercise: static low angle squat

[1]months 1-6: center based, months 7-18: center+home or home based, home based: Thera-Band exercise program; [2]months 1-4: center based; months 5-18: center, home or center+home based; [3]Information obtained from author; [4]age related heart rate according Karvonen formula; [5]1RM determined by 5-7 RM test; [6]1RM determined by 5 RM test (3 months before intervention); **h**=hour; **MF**= maximal force (determined by 10 RM-test); **mo**=month; **mph**=mile per hour; **NA**= not available; **OKC-ex**= Open kinematic chain exercises, **reps**=repetitions; **s**=seconds; **T**= training; **wk**=week; **HRR**= heart rate reserve; **HRmax**= maximum heart rate; **y**= year

Table 3:
Detailed individual results

Reference Study design	Population Sample size: N (% retention) Female: % (% retention) Male: % (% retention) Age (years)	Number of study arms / (G) Interventions for each arm	Intervention period	Sampling	Results	Effect size
CRP Basal effects						
Nicklas et al., 2004 RCT	OAk (Rx) N=316 (79.7%) Female[16]: 71.7% (NA)[1] Male[16]: 28.9% (NA)[1] (G1) 69 ± 6[6] (G2) 68 ± 7[6] (G3) 68 ± 5[6] (G4) 69 ± 6[6]	4/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet (G4) Control: healthy lifestyle 1h, 3x/week: Aerobic (walking 15 min, 50-75%HRR), resistance training (2x12 repetitions, 15 min), aerobic (15 min), cooling down (15 min)	18mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo	**Between group differences: G1 vs G2 vs G3 vs G4** T0: ND: 6.8 ± 7.8 vs 6.5 ± 7.9 vs 6.0 ± 6.5 vs 5.9 ± 6.0 µg/mL[2] ΔCRP T0 - T1: -0.07 ± 0.42 vs -0.11 ± 0.52 vs -0.11 ± 0.72 vs 0.08 ± 0.63 µg/mL[2] T0 - T2: -0.02 ± 0.47 vs -0.18 ± 0.54 vs-0.13 ± 0.53 vs 0.35 ± 1.9 µg/mL[2] G1: ND (p=0.57) G3↓ vs (G1 + G4) (Δ log CRP: -0.26 ± (0.07) vs 0.04 ± (0.07) µg/mL (p=0.01))	
Samut et al., 2015 RCT	OAk (Sx+Rx) N=42 (95%) Female: 90% (NA) Male: 10% (NA) (G1) 62.46± 7.71[6] (G2) 57.57 ± 5.79[6] (G3) 60.92 ± 8.85[6]	3/ (G1) Strength (isokinetic) (G2) Aerobic (G3) Info disease & recommendations about precautions Strength: 3x/week 5 min warm-up on treadmill 5 concentric flexion and extension exercises Aerobic: 3x/week 5 min warm-up on treadmill Week 1-4: 65-70% of age related HR Week 5-6: 70-75% of age related HR 5 min cool-down period	6wks	Serum (T0) at baseline (T1) at 6 wks	**Between group differences: G1 vs G2 vs G3** T0: ND: 0.302 (0.100 - 1.600) vs 0.488 (0.105 - 1.450) vs 0.386 (0.159 - 1.170) mg/L (p=0.460) T1: 0.229 (0.100 - 0.785) vs 0.432 (0.127 - 0.875) vs 0.381 (0.100 - 1.190) mg/L[2] **Within group differences: T0 vs T1** G1: ND: (0.302 (0.100 - 1.600) vs 0.229 (0.100 - 0.785) mg/L (p= 0.087) G2: ND: (0.488 (0.105 - 1.450) vs 0.432 (0.127 - 0.875) mg/L (p= 0.072) G3: ND: (0.386 (0.159 - 1.170) vs 0.381 (0.100 - 1.190) mg/L (p= 0.382)	
hsCRP	OAk (NA)	2/	4-6 wks	Blood	**Between group differences: G1 vs G2**	i.d.a.
Kim et al., 2021 RCT	N= 43 (98%) Female: 19 (44%) Male: 24 (56%) (G1) 67.4 ± 6.0 (G2) 66.9 ± 6.3	(G1) Strength (i.e. aquatic exercises) (G2) Control: usual care + brochure on perioperative nutrition 3x/week 60 min until scheduled total knee arthroplasty surgery (4-8 weeks) 10 min warm-up, 20 min flexibility and strength, 20 min low intensity endurance, 10 min cool down. Resistance equipment (i.e. ankle cuffs) was added depending on the tolerance to increase intensity		(T0) at baseline (T1) 1 week before TKA surgery	T0: ND: 5.72 ± 7.48 vs 2.37 ± 3.57 [2] **SMD:** Log(hsCRP): -0.25 [95% CI: -0.69 to 0.20] (p=0.27)	
Germanou et al., 2013 NRUCT	(G1) OAk (Sx+Rx) N=10 (100%) Female[16] :100% (100%) 58.9 ± 5.9 yrs (G2) Healthy Knees N=10 (100%) Female[16]: 100% (100%) 62.4 ± 5.1	2/ Strength (i.e. isokinetic exercises) 6 sets of 10 maximal concentric knee extensions/flexions	24h	Serum (T0) at baseline (T1) 24h post-exercise	**Between group differences: G1 vs G2** T0: G1↑ vs G2[4] (p=0.001) T1: G1↑ vs G2[4] (p=0.001) **Within group differences: T0 vs T1** G1: ND[2][4]; 4.54 ± (0.39) vs 4.60 ± (0.58) mg/L[5] G2: ND[2][4]; 2.67 ± (0.23) vs 2.73 ± (0.39) mg/L[5]	ES_{G1}= 0.039
Beavers et al. 2014 RCT	OAk (Sx+Rx) N=454 (78%) Female [16]: 71.3% (NA)[1] Male[16]: 28.7% (NA)[1] 65.6 ± 6.2	3/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet 1h 3x/week: Aerobic (walking 15 min), strength training (20 min), aerobic phase (15 min), cooling down (10 min)	18mo	Plasma (T0) at baseline (T1) at 6 mo (T2) at 18 mo (at least 24h after last acute bout of exercise)	**Within group differences: T0 vs T1** G1: ND: (0.302 (0.100 - 1.600) vs 0.229 (0.100 - 0.785) mg/L (p= 0.087) G2: ND: (0.488 (0.105 - 1.450) vs 0.432 (0.127 - 0.875) mg/L (p= 0.072) G3: ND: (0.386 (0.159 - 1.170) vs 0.381 (0.100 - 1.190) mg/L (p= 0.382)	
CRP Acute effects						
Germanou et al., 2013	(G1) OAk (Sx+Rx) N=10 (100%) Female[16]: 100% (100%)	2/ Strength (i.e. isokinetic exercises)	<24 h (1 x)	Serum	**Between group differences: G1 vs G2** T0: G1↑ vs G2[4] (p=0.001)	

	(G2) Healthy Knees N=10 (100%) Female[16]: 100% (100%) 62.4 ± 5.1	6 sets of 10 maximal concentric knee extensions/flexions		(T1) immediately post-exercise	**Within group differences: T0 vs T1** G1: ND[2][4]; 4.54 ± (0.39) vs 4.63 ± (0.70) mg/L[5] G2: ND[2][4]; 2.67 ± (0.23) vs 2.76 ± (0.51) mg/L[5]	ES_{G1}= 0.052
CRPM Basal effects						
Loeser et al., 2017 RCT	OAk (Sx+Rx) N= 429 (94.49%) Female [16]: 100% (NA) 65.76 ± 6.22 yrs	3/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet 1h, 3x/week: Aerobic (walking 15 min), strength training (20 min), aerobic phase (15 min), cooling down (10 min)	18mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo (at least 24h after last acute bout of exercise)	Secondary analysis data IDEA- trial **Between group differences: G1 vs G2 vs G3: ND[2]** T2[20] -T0: log(CRPM)= -0.08 ± (0.03) (-0.84%) vs -0.11 ± (0.03) (-1.12%) vs -0.08 ± (0.03) (-0.83%)	
					Within group differences: T0 vs T1 vs T2: ND[2][4]	
IL-1β Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA)[1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1): Aerobic (i.e. cycling) (G2): Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 57 ± (9) vs 48 ± (8) pg/mL[2] G2: ND: 38 ± (5) vs 37 ± (4) pg/mL[2]	ES_{G1}= -0.237 ES_{G2}= -0.050
Zhao et al., 2019 RCT	OAk (Sx) N= 55 Female: [4] Male: [4] (54-65)	2/ (G1): Strength (i.e. static low angle squat) (G2): Control (NA) 2x/day 30 min static low angle squats	2 y	Synovial fluid (OA knee) (T0) at baseline (T1) after 12 months	**Within group differences: T0 vs T1** G1: ↓: 80.23 ± 6.54 vs 43.75 ± 5.23 pg/mL (p<0.001)	ES_{G1}= -6.199
Armagan et al., 2012 RCT	OAk (Sx+Rx) N= 55 (90.91%) Female: 100% (NA)[1] (G1) 63.30 ± 6.45 (G2) 59.85 ± 6.67	2/ (G1) Strength + calcitonin treatment (G2) Strength 1x/day 2 sets of 20 repetitions with 2 min rest between each set at home	6 mo	Serum (T0) at baseline (T1) at 6 months	**Between group differences: G1 vs G2** T0: ND: 2.36 (2.00-2.85) vs 2.06 (1.84-2.39) (p= 0.354) T1: ND: 2.16 (2.02 -2.72) vs 2.19 (1.60-3.00) (p=0.205)	ES_{T1}= 0,049
					Within group differences: T0 vs T1 G1: ND: 2.36 (2.00-2.85) vs 2.16 (2.02 - 2.72) (p=0.301) G2: ND: 2.06 (1.84 -2.39) vs 2.19 (1.60-3.00) (p=0.235)	ES_{G2}= 0.146
Messier et al., 2000 RCT	OAk (Rx) N=24 (87.5%) Female[16]: 70.8% (NA) Male[16]: 29.2% (NA) (G1) 69 ± 5[6] (G2) 67 ± 4[6]	2/ (G1) Aerobic + strength (G2) Diet+ aerobic+ strength 3x/week, 1h/day 5 min warm-up, 10 min walking (50-75% HRR), 20-30 min strength training, 10 min walking (50-75% HRR), 5 min cool-down	6 mo	Synovial fluid (most symptomatic knee joint) (T0) at baseline (T1) at 6 mo	**Combined data for two intervention groups ("within group"):** T0 vs T1↓ ; 25.325 ± (9.75) vs 8.306 ± (6.112) pg/mL (p<0.04)[12]	
IL-2 Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA)[1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1): Aerobic (i.e. cycling) (G2): Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 56 ± (10) vs 71 ± (10) pg/mL[2] G2: ND: 49 ± (9) vs 41 ± (8) pg/mL[2]	ES_{G1}= 0.335 ES_{G2}= -0.175
IL-4 Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA)[1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1): Aerobic (i.e. cycling) (G2): Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 45 ± (7) vs 38 ± (4) pg/mL[2] G2: ND: 45 ± (7) vs 36 ± (4) pg/mL[2]	ES_{G1}= -0.285 ES_{G2}= -0.366
IL-5 Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA) [1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1) Aerobic (i.e. cycling) (G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 62 ± (5) vs 57 ± (6) pg/mL[2] G2: ND: 39 ± (3) vs 39 ± (4) pg/mL[2]	ES_{G1}= -0.203 ES_{G2}= -0.000
IL-6 Basal effects						
Nicklas et al., 2004 RCT	OAk (Rx) N=316 (79.7%) Female[16]: 71.7% (NA)[1] Male[16]: 28.9% (NA)[1] (G1) 69 ± 6[6] (G2) 68 ± 7[6]	4/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet (G4) Control: healthy lifestyle	18 mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo	**Between group differences: G1 vs G2 vs G3 vs G4** T0: ND: 4.4 ± 3.1 vs 4.9 ± 3.0 vs 4.7 ± 3.4 vs 4.7 ± 3.2 pg/mL[2] Δ IL-6 T0 - T1: 0.15 ± 1.8 vs -0.35 ± 2.15 vs -	

	(G3) 68 ± 5[6] (G4) 69 ± 6[6]	1h 3x/week: Aerobic (walking 15 min, 50-75%HRR), resistance training (2x12 repetitions, 15 min), aerobic (15 min), cooling down (15 min)			0.51 ± 2.1 vs 0.19 ± 2.8 pg/mL[2] T0 - T2: 0.02 ± 2.4 vs -0.35 ± 1.8 vs -0.71 ± 2.4 vs 0.27 ± 2.8 pg/mL[2] G1: ND (p=0.86) G3 ↓ (p=0.009) G3 ↓ vs (G1 + G4) (Δ log IL-6: -0.13 ± (0.04) vs -0.01 ± (0.04) pg/mL)[2]	
Samut et al., 2015 RCT	OAk (Sx+Rx) N=42 (95%) Female:90% (NA) Male: 10% (NA) (G1) 62.46± 7.71[6] (G2) 57.57 ± 5.79[6] (G3) 60.92 ± 8.85[6]	3/ (G1) Strength (isokinetic) (G2) Aerobic (G3) Control: info disease & recommendations about precautions Strength: 3x/week 5 min warm-up on treadmill 5 concentric flexion and extension exercises Aerobic: 3x/week 5 min warm-up on treadmill Week 1-4: 65-70% of age related HR Week 5-6: 70-75% of age related HR 5 min cool-down period	6 wks	Serum (T0) at baseline (T1) at 6 wks	**Between group differences: G1 vs G2 vs G3** T0: 0.732 (0.037 - 2.497) vs 0.861 (0.173 - 1.894) vs 0.259 (0.037 - 1.507) pg/mL (p=0.113) T1: 0.947 (0.037 - 6.044) vs 0.625 (0.037 - 2.024) vs 0.381 (0.037 - 1.259) pg/mL[2] **Within goup differences: T0 vs T1** G1: ND: (0.732 (0.037 - 2.497) vs 0.947 (0.037 - 6.044) pg/mL, (p=0.753) G2: ND: (0.861 (0.173 - 1.894) vs 0.625 (0.037 - 2.024) pg/mL, (p= 0.706) G3: ND: (0.259 (0.037 - 1.507) vs 0.381 (0.037 - 1.259) pg/mL, (p=0.583)	
Germanou et al., 2013 NRCT	(G1) OAk (Sx+Rx) N=10 (100%) Female[16]: 100% (100%) 58.9 ± 5.9 (G2) Healthy Knees N=10 (100%) Female[16]: 100% (100%) 62.4 ± 5.1	2/ Strength (i.e. isokinetic exercises) 6 sets of 10 maximal concentric knee extensions/flexions	24h	Serum (T0) at baseline (T1) 24 h post-exercise	**Between group differences: G1 vs G2** T0: G1↑ vs G2[4] (p=0.04) T1: G1↑ vs G2[4][8] (p=0.04) **Within group differences T0 vs T1:** G1: ND[2][4][8] ; 4.85 ± (0.70) vs 4.92 ± (0.58) pg/mL[5] G2: ND[2][4][8] ; 3.87 ± (0.42) vs 3.94 ± (0.49) pg/mL[5]	 ES_{G1}= 0.035
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic (walking) 3x/week 5min warm up walking from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down	12 wks	Plasma In the morning (T0) at baseline (T1) at 12 wks	**Within group differences:** T0 vs T1: ND; 1.7 ± 2.8 [-0.02 to 3.5] vs 1.2 ± 0.8 [0.8 to 1.7] pg/mL (p>0.05) Cohen's d=0.343	ES_{G1}= -0.278
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA) [1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1) Aerobic (i.e.cycling) (G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1 ↓: 90 ± (10) vs 79 ± (9) pg/mL, (p<0.05) G2 ↓: 100 ± (11) vs 76 ± (7) pg/mL, (p<0.05)	ES_{G1}= -0.259 ES_{G2}= -0.596
Aguiar et al., 2014 NRUCT	OAk (Sx+Rx) N=27 (81.5%) Female: NA (81.8%) Male: NA (18.2%) 58.8 ± 6.4	1/ Other: Flexibility + strength 3x/week, 80min/day Supervised Week 1-4: 60% of max. load Week 5-8: 70% max. load Week 9-12: full weight determined by 10-MR test	12 wks	Serum (T0) at baseline (T1) at 12 wks (change after training)	**Within group differences:** T0 vs T1↓[4] (p<0.001); 1.96 (17) vs 1.37 [0.09 - 3.77] pg/mL[5][12]	$ES_{T1\text{-}T0}$= -0.513
Kim et al., 2021 RCT	OAk (NA) N= 43 (98%) Female: 19 (44%) Male: 24 (56%) (G1) 67.4 ± 6.0 (G2) 66.9 ± 6.3	2/ (G1) Strength (i.e. aquatic exercises) (G2) Control: usual care + brochure on perioperative nutrition 3x/week 60 min until scheduled total knee arthroplasty surgery (4-8 weeks) 10 min warm-up, 20 min flexibility and strength, 20 min low intensity endurance, 10 min cool down. Resistance equipment (i.e. ankle cuffs) was added depending on the tolerance to increase intensity	4-6 wks	Blood (T0) at baseline (T1) 1 week before TKA surgery	**Between group differences: G1 vs G2** T0: ND: 4.16 ± 4.04 vs 2.68 ± 2.46 [2] **SMD:** Log (IL-6): -0.02 [95% CI: -0.32 to 0.28] (p=0.90)	i.d.a.
Messier et al., 2013 RCT	OAk (Sx+Rx) N=454 (88%)[17] Female: 71.6% (NA) Male: 28.4% (NA) 66.6 ± 6	3/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet 1h/day, 3x/week: 15 min walking 20 min strength training 15 min aerobic exercises 10 min cool-down	18 mo	Plasma (T0) at baseline (T1) at 6 mo (T2) at 18 mo (at least 24h after last acute bout of exercise)	N=Results for Multiple imputation-based Model (50 Multiply imputed data sets) **Between group differences: G1 vs G2 vs G3 (p=0.008)** T0: 3.0 [2.6 to 3.3] vs 3.2 [2.9 to 3.6] vs 3.2 [2.8 to 3.6] pg/mL T1: 2.9 [2.6 to 3.3] vs 2.8 [2.5 to 3.2] vs 2.7 [2.4 to 3.1] pg/mL T2: 3.0 [2.7 to 3.3] vs 2.7 [2.4 to 3.1] vs 2.7 [2.3 to 3.0] pg/mL T2[9]: 3.1 [2.9 to 3.4] vs 2.7 [2.5 to 3.0]	

					vs 2.7 [2.4 to 3.0] pg/mL **Pairwise between-groups differences at T2[9][10]** G1 vs G2: 0.39[-0.03 to 0.81] pg/mL (p=0.007) G1 vs G3: 0.43[0.01 to 0.85] pg/mL (p=0.006) G3 vs G2:-0.04[-0.47 to 0.40] pg/mL (p=0.98)	
					Within group differences: ΔT0 vs T2 G1: 0.1 pg/mL: no reduction (0%) G2: -0.5 pg/mL: reduction of 15% G3: -0.5 pg/mL: reduction of 16%	
IL-6 Acute effects						
Germanou et al., 2013 NRCT	(G1) OAk (Sx+Rx) N=10 (100%) Female[16]: 100% (100%) 58.9 ± 5.9 (G2) Healthy Knees N=10 (100%) Female[16]: 100% (100%) 62.4 ± 5.1	2/ Strength (i.e. isokinetic exercises) 6 sets of 10 maximal concentric knee extensions/flexions	<24 h (1 x)	Serum (T0) at baseline (T1) immediately post-exercise	**Between group differences: G1 vs G2** T0: G1↑ vs G2[4] (p=0.04) T1: G1↑ vs G2[2][4][8]	
					Within group differences T0 vs T1: G1↑[4] (p=0.04); 4.85 ± (0.70) vs 5.50 ± (0.61) pg/mL[5] G2: ND[2][4][8]; 3.87 ± (0.42) vs 4.01 ± (0.70) pg/mL[5]	ES_{G1}= 0.314
Helmark et al., 2010 RCT	OAk (Sx+Rx) N=31 (93.5%) Female: 100% (100%) (G1) 66 ±6 (G2) 67 ± 7	2/ (G1) Strength (G2) Control: non exercise 5 min warm-up on bicycle 25 sets of 10 repetitions at 60% of 1RM on legg-press machine	<24h (1x)	Synovial fluid: - peri-synovial - intra-articular at latest 1h after exercise; 6 samples every 30' (3h); samples were later pooled: T1= sample 1 to 3 (30', 60', 90'); T2 = sample 4 to 6 (120', 150', 180')	**Between group differences:** T1: G1 vs G2: ND [2][4]	
					Within group differences T1 vs T2: Intra-articular: G1↑ (p<0.05)[4][8] G2↑ (p<0.05)[4][8] peri-synovial: G1↑ (p<0.05)[4][8] G2↑ (p<0.05)[4][8]	
Helmark et al., 2012 NRUCT	OAk (Sx+Rx) N=11 (63.6%) Female: NA Male: NA 61 ± 11	1/ Strength 30min one-legged extension at 60% 1RM, 10 sets of 8 repetitions	<24h (1x)	Synovial fluid (knee with most severe symptoms) (T0) at baseline (± 3 mo before exercise intervention)	**Within group differences T0 vs T1:** ND [2][4][18]; 97.96 (22.53-253.27) vs 149.66 (23.20 -612.26) pg/mL[5]	$ES_{T1\text{-}T0}$: 0.9
				(T1) 15-30' after exercise		
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic 3x/week 5min warm up walking from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down	12 wks	Plasma (T0) at baseline: (T00) pre-acute EX (T01) post-acute EX (T02) 30' post-acute EX (T1) at 12 wks: (T10) pre-acute EX (T11) post-acute EX (T12) 30' post-acute EX	**Within group differences:** i.d.a. ND [2][4][11][18]	
IL-6sR Basal effects						
Nicklas et al., 2004 RCT	OAk (Rx) N=316 (79.7%) Female[16]: 71.7% (NA)[1] Male[16]: 28.9% (NA)[1] (G1) 69 ± 6 (G2) 68 ± 7 (G3) 68 ± 5 (G4) 69 ± 6	4/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet (G4) Control: healthy lifestyle 1h 3x/week: Aerobic (walking 15 min, 50-75%HRR), resistance training (2x12 repetitions, 15 min), aerobic (15 min), cooling down (15 min)	18 mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo	**Between group differences: G1 vs G2 vs G3 vs G4** T0: ND: 34581 ± 9596 vs 35156 ± 11075 vs 35197 ± 8911 vs 38040 ± 10764 pg/mL[2] Δ IL-6sR T0 - T1: -856 ± 5135 vs -759 ± 3235 vs -838 ± 3645 vs -1247 ± 5159 pg/mL[2] T0 - T2: 94 ± 4399 vs -746 ± 4166 vs -1522 ± 8344 vs -739 ± 4910 pg/mL[2] G1: ND (p=0.44) G3: ND (p=0.81) IL-6/IL-6sR G1: ND[2] G3: ND[2]	
IL-7 Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA) [1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1) Aerobic (i.e. cycling) (G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 53±(6) vs 48±(6) pg/mL[2] G2: ND: 45±(5) vs 42 ± (6) pg/mL[2]	ES_{G1}= -0.186 ES_{G2}= -0.122
IL-8 Basal effects						
Alkatan et al., 2016	OAk (Sx + Rx) N= 48 (83.33%)[17]	2/ (G1) Aerobic (i.e. cycling)	12 wks	Plasma	**Within group differences: T0 vs T1** G1: ND: 260 ± (34) vs 275 ± (35) pg/mL[2]	ES_{G1}= 0.097

RCT	Female: 91.67% (NA)[1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	(G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR		(T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	G2: ND: 225 ± (22) vs 241 ± (14) pg/mL[2]	ES_{G2}= 0.199
IL-8 Acute effects						
Helmark et al., 2010 RCT	OAk (Sx+Rx) N=31 (93.5%) Female: 100% (100%) (G1) 66 ±6 (G2) 67 ± 7	2/ (G1) Strength (G2) Control: non exercise 5 min warm-up on bicycle 25 sets of 10 repetitions at 60% of 1RM on legg-press machine	<24h (1x)	Synovial fluid: - peri-synovial - intra-articular At latest 1h after exercise; 6 samples every 30' (3h); samples were later pooled: T1= sample 1 to 3 (30', 60', 90') T2 = sample 4 to 6 (120', 150', 180')	**Between group differences G1 vs G2:** T1: ND[2][4] **Within group differences T1 vs T2:** Intra-articular: G1↑ (p<0.05)[4][8] G2↑ (p<0.05)[4][8] peri-synovial: G1↑ (p<0.05)[4][8] G2↑ (p<0.05)[4][8]	
IL-10 Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA) [1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1) Aerobic (i.e. cycling) (G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 152 ± (43) vs 155 ± (46) pg/mL[2] G2: ND: 105 ± (7) vs 95 ± (7) pg/mL[2]	ES_{G1}= 0.015 ES_{G2}= -0.319
Zhao et al., 2019 RCT	OAk (Sx) N= 55 Female: [4] Male: [4] (54-65)	2/ (G1): Strength (i.e. static low angle squat) (G2): Control (NA) 2x/day 30 min static low angle squats	2 y	Synovial fluid (OA knee) (T0) at baseline (T1) after 12 months	**Within group differences: T0 vs T1** G1: ↑: 45.14 ± 5.36 vs 90.45 ± 4.53 pg/mL (p<0.001)	ES_{G1}= 9.163
IL-10 Acute effects						
Helmark et al., 2010 RCT	OAk (Sx+Rx) N=31 (93.5%) Female: 100% (100%) (G1) 66 ±6 (G2) 67 ± 7	2/ (G1) Strength (G2) Control: non exercise 5 min warm-up on bicycle 25 sets of 10 repetitions at 60% of 1RM on legg-press machine	<24h (1x)	Synovial fluid: - peri-synovial - intra-articular At latest 1h after exercise; 6 samples every 30' (3h); samples were later pooled: T1= sample 1 to 3 (30', 60', 90') T2 = sample 4 to 6 (120', 150', 180')	**Between group differences G1 vs G2:** T1: ND[2][4] **Within group differences T1 vs T2:** Intra-articular: G1↑ (p<0.05)[4][8] G2: ND[2][4][8] peri-synovial: G1↑(p<0.05)[4][8] G2: ND[2][4][8]	
IL-12 Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA) [1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1) Aerobic (i.e. cycling) (G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 48 ± (8) vs 53 ± (10) pg/mL[2] G2: ND: 48 ± (10) vs 41 ± (7) pg/mL[2]	ES_{G1}= 0.124 ES_{G2}= -0.184
IL-13 Basal effects						
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA) [1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1) Aerobic (i.e. cycling) (G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 50 ± (10) vs 46 ± (7) pg/mL[2] G2: ND: 37 ± (6) vs 31 ± (3) pg/mL[2]	ES_{G1}= -0.105 ES_{G2}= -0.298
TNF-α Basal effects						
Nicklas et al., 2004 RCT	OAk (Rx) N=316 (79.7%) Female[16]: 71.7% (NA)[1] Male[16]: 28.9% (NA)[1] (G1) 69 ± 6[6] (G2) 68 ± 7[6] (G3) 68 ± 5[6] (G4) 69 ± 6[6]	4/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet (G4) Control: healthy lifestyle 1h, 3x/week: Aerobic (walking 15 min, 50-75%HRR), resistance training (2x12 repetitions, 15 min), aerobic (15 min), cooling down (15 min)	18 mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo	**Between group differences: G1 vs G2 vs G3 vs G4** T0: ND: 3.4 ± 4.8 vs 3.4 ± 6.4 vs 2.5 ± 1.8 vs 3.8± 7.5 pg/mL[2] ΔTNF-α T0 - T1: -0.69 ± 5.8 vs -0.46 ± 3.7 vs -0.23 ± 1.8 vs -0.74 ± 3.7 pg/mL[2] T0 - T2: 0.28 ± 6.3 vs -0.72 ± 4.6 vs 0.64 ± 5.9 vs -0.77 ± 3.7 pg/mL[2] G1: ND (p=0.30) G3: ND (p=0.67) TNF-α/sTNFR1, TNF-α/sTNFR2, TNF-α/sTNFR1+sTNFR2 G1: ND[2] G2: ND[2]	
Samut et al., 2015 RCT	OAk (Sx+Rx) N=42 (95%) Female:90% (NA) Male: 10% (NA) (G1) 62.46± 7.71[6] (G2) 57.57 ± 5.79[6] (G3) 60.92 ± 8.85[6]	3/ (G1) Strength (isokinetic) (G2) Aerobic (G3) Control: info disease & recommendations precautions Strength: 3x/week	6 wks	Serum (T0) at baseline (T1) at 6 wks	**Between group differences: G1 vs G2 vs G3** T0: 0.446 (0.038 - 2.674) vs 1.310 (0.038 - 3.789) vs 0.038 (0.038 - 1.282) pg/mL, (p<0.001) T1: 0.223 (0.038 - 3.064) vs 0.753 (0.038 - 0.351) vs 0.038 (0.038 - 1.895) pg/mL[2]	

		5 min warm-up on treadmill 5 concentric flexion and extension exercises Aerobic: 3x/week 5 min warm-up on treadmill Week 1-4: 65-70% of age related HR Week 5-6: 70-75% of age related HR 5 min cool-down period				
					Within goup differences: T0 vs T1 G1: ND (0.446 (0.038 - 2.674) vs 0.223 (0.038 - 3.064) pg/mL, (p=0.576) G2: ND (1.310 (0.038 - 3.789) vs 0.753 (0.038 - 0.351) pg/mL, (p=0.414) G3: ND (0.038 (0.038 - 1.282) vs 0.038 (0.038 - 1.895) pg/mL, (p=0.500)	
Kim et al., 2021 RCT	OAk (NA) N= 43 (98%) Female: 19 (44%) Male: 24 (56%) (G1) 67.4 ± 6.0 (G2) 66.9 ± 6.3	2/ (G1) Strength (i.e. aquatic exercises) (G2) Control: usual care + brochure on perioperative nutrition 3x/week 60 min until scheduled total knee arthroplasty surgery (4-8 weeks) 10 min warm-up, 20 min flexibility and strength, 20 min low intensity endurance, 10 min cool down. Resistance equipment (i.e. ankle cuffs) was added depending on the tolerance to increase intensity	4-6 wks	Blood (T0) at baseline (T1) 1 week before TKA surgery	**Between group differences: G1 vs G2** T0: ND: 1.38 ± 0.58 vs 2.85 ± 6.43 [2] **SMD:** Log(TNF-α): 0.10 [95% CI: -0.07 to 0.26] (p=0.25)	i.d.a.
Zhao et al., 2019 RCT	OAk (Sx) N= 55 Female: [4] Male: [4] (54-65)	2/ (G1): Strength (i.e. static low angle squat) (G2): Control (NA) 2x/day 30 min static low angle squats	2 y	Synovial fluid (OA knee) (T0) at baseline (T1) after 12 months	**Within group differences: T0 vs T1** G1: ↓: 22.43 ± 4.31 vs 14.07 ± 2.89 pg/mL (p<0.001)	ES_{G1}= -2.322
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic 3x/week 5min warm up	12 wks	Plasma	**Within group differences:** T0 vs T1: ND; 37.8 ± 20.1[-6.0 to 81.63] vs 72.0 ± 105.2[8.4 to 135.6] pg/mL;	ES_{G1}= 0.546
		walking from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down		(T0) at baseline (T1) at 12 wks	(p>0.05); Cohen's d=0.638	
Alkatan et al., 2016 RCT	OAk (Sx + Rx) N= 48 (83.33%)[17] Female: 91.67% (NA)[1] Male: 8.33% (NA)[1] (G1) 61 ± 1 (G2) 59 ± 2	2/ (G1) Aerobic (i.e. cycling) (G2) Aerobic (i.e. swimming) From 20-30 min 3x/week at 40-50% HRR to 40-50min 3x/week at 60-70% HRR	12 wks	Plasma (T0) at baseline (T1) at week 12 (at least 48h after last exercise session)	**Within group differences: T0 vs T1** G1: ND: 264 ± (26) vs 253 ± (25) pg/mL[2] G2: ND: 246 ± (23) vs 236 ± (23) pg/mL[2]	ES_{G1}= -0.096 ES_{G2}= -0.097
Aguiar et al., 2014 NRUCT	OAk (Sx+Rx) N=27 (81.5%) Female: NA (81.8%) Male: NA (18.2%) 58.8 ± 6.4	1/ Other: Flexibility + strength 3x/week, 80min/day Supervised Week 1-4: 60% of max. load Week 5-8: 70% max. load Week 9-12: full weight determined by 10-MR test	12 wks	Serum (T0) at baseline (T1) at 12 wks Change after training	**Within group differences:** T0 vs T1: ND[2][4]; 113.05 [0 – 695.12] vs 127.57 [0 – 751.52] pg/mL[5][12]	ES_{T1-T0}= 0.080
TNF-α Acute effects						
Helmark et al., 2010 RCT	OAk (Sx+Rx) N=31 (93.5%) Female: 100% (100%) (G1) 66 ±6 (G2) 67 ± 7	2/ (G1) Strength (G2) Control: non exercise 5 min warm-up on bicycle 25 sets of 10 repetitions at 60% of 1RM on legg-press machine	<24h (1x)	Synovial fluid: - peri-synovial - intra-articular At latest 1h after exercise; 6 samples every 30' (3h); samples were later pooled: T1= sample 1 to 3 (30', 60', 90') T2 = sample 4 to 6 (120', 150', 180')	**Between group differences G1 vs G2:** T1: ND[2][4]	
					Within group differences T1 vs T2: Intra-articular: G1↑ (p<0.05)[4][8] G2↑ (p<0.05)[4][8] peri-synovial: G1↑ (p<0.05)[4][8]	
Jayabalan et al., 2019 NRUCT	OAk (Sx+Rx) N= 27 (100%) Female: 74.07% (100%) Male: 25.93% (100%) 63.5 ± 7.7	2/ (G1) Aerobic: continuous walking (G2) Aerobic: interval walking 40-60% HRR; 1.3m/sec on treadmill	45 min (x2)	Serum (T0) at baseline (T1) after 15 min (T2) after 30 min (T3) after 45 min Sampling of interval walking was	**Between group differences G1 vs G2** T0: ND[8] 11.06 ± 7.10 vs 9.72 ± 6.38 ng/mL[2] T1: 9.66 ± 4.79 vs 9.31 ± 4.77 ng/mL[2] T2: 10.52 ± 5.55 vs 10.34 ± 5.21 ng/mL[2] T3: 10.93 ± 6.38 vs 10.24 ± 6.52 ng/mL[2]	

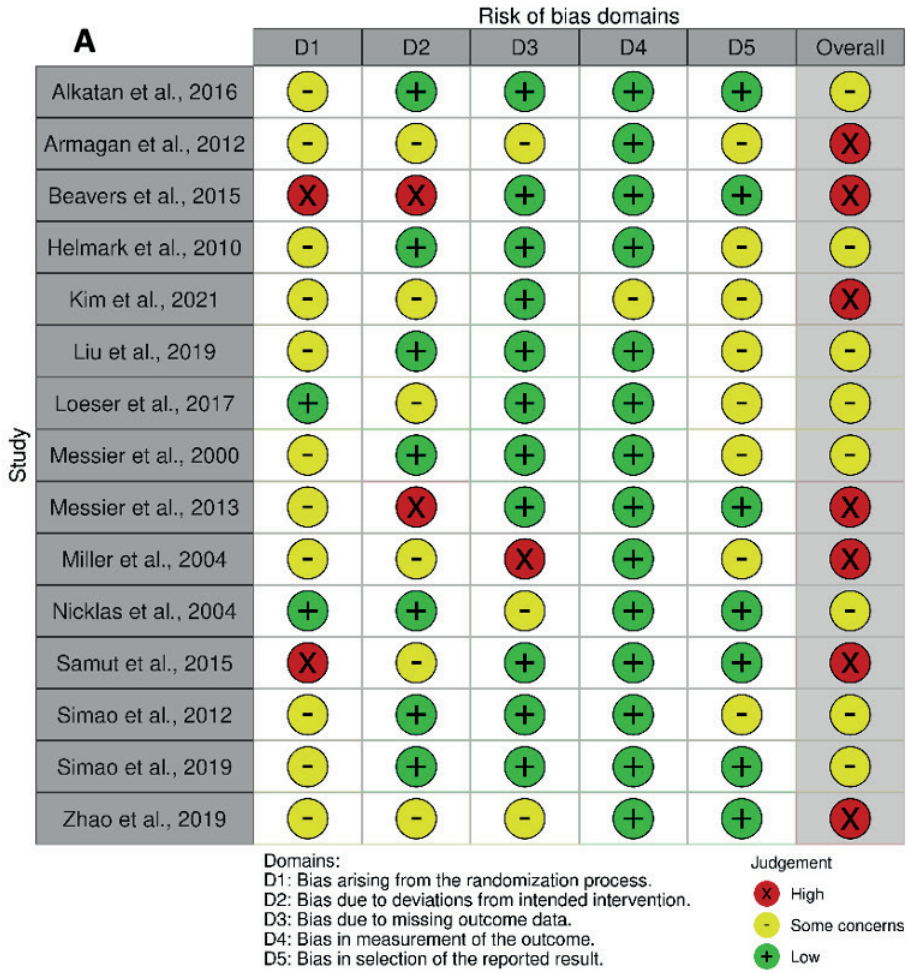
				performed at least 72h after sampling continuous walking		
					Within group differences: T0 vs T1 vs T2 vs T3: G1: 11.06 ± 7.10 vs 9.66 ± 4.79 vs 10.52 ± 5.55 vs 10.93 ± 6.38 ng/mL[2] G2: 9.72 ± 6.38 vs 9.31 ± 4.77 vs 10.34 ± 5.21 vs 10.24 ± 6.52 ng/mL[2] **Within group differences in increase from baseline** G1 : T1 vs T0: ND: (p=0.196) T2 vs T0: ND: (p=0.372) T3 vs T0: ND: (p=0.472) G2 : T1 vs T0: ND: (p= 0.387) T2 vs T0: ND: (p=0.339) T3 vs T0: ND: (p=0.385)	ES_{G1}= -0.019 ES_{G2}= 0.081
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic 3x/week 5min warm up Walking from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down	12 wks	Plasma (T0) at baseline: (T00) pre-acute EX (T01) post-acute EX (T02) 30' post-acute EX (T1) at 12 weeks: (T10) pre-acute EX (T11) post-acute EX (T12) 30' post-acute EX	**Within group differences:** ND: i.d.a. [2][4][11][18]	
sTNFR1 Basal effects						
Nicklas et al., 2004 RCT	OAk (Rx) N=316 (79.7%) Female[16]: 71.7% (NA)[1] Male[16]: 28.9% (NA)[1] (G1) 69 ± 6 (G2) 68 ± 7 (G3) 68 ± 5 (G4) 69 ± 6	4/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet (G4) Control: healthy lifestyle 1h 3x/week: Aerobic (walking 15 min, 50-75%HRR), resistance training (2x12 repetitions, 15 min),	18 mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo	**Between group differences: G1 vs G2 vs G3 vs G4** T0: ND: 1433 ± 404 vs 1395 ± 397 vs 1409 ± 470 vs 1464 ± 421 pg/mL[2] ΔsTNFR1 T0 - T1: -38 ± 224 vs -80 ± 226 vs -92 ± 290 vs -10 ± 291 pg/mL[2] T0 - T2: 25 ± 252 vs -3 ± 241 vs -34 ± 362 vs 62 ± 312 pg/mL[2] G1: ND, (p=0.54) G3↓ vs (G1 + G4) (Δlog sTNFR1:	
		aerobic (15 min), cooling down (15 min)			-0.070 ± (0.017) vs -0.013 ± (0.017) pg/mL), (p=0.007)	
Simao et al., 2012 RCT	OAk (Sx+Rx) N=35 (91.4%) Female: NA (87.5%) Male: NA (12.5%) (G1) 75 ± 7.4 (G2) 69 ± 3.7 (G3) 71 ± 5.3	3/ (G1) Strength (squat on vibration platform) (G2) Strength (squat) (G3) Control: no change of lifestyle 3x/week Volume of squat training was increased by increasing the time and number of sets and reducing rest time 10 min warm up on a bike at 70%HRmax	12 wks	Plasma (T0) at baseline (T1) at 12 wks	**Between group differences G1 vs G2 vs G3:** T0: 1033.0 «718-1281» vs 722.4 «522-1052» vs 682.8 «617-849» pg/mL[2] T1: 709.2 «379-1281» vs 742.5 «373 - 1492» vs 1072.0 «879 - 1252» pg/mL[2] **ΔPOST-hoc between:** G2 vs G1:ND: p>0.05 G3 vs G1↓: SD: p<0.01 G3 vs G2: ND: p>0.05	
					Within group differences Δ T0 vs T1 [13] : G1 ↓: -146.0 «-826 to 183»pg/mL, (p=0.04) G2: ND: 155.0 «-720 to 536» pg/mL, (p=0.95) G3 ↑: 389.2 «102 to 638» pg/mL, (p=0.001)	
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic 3x/week 5min warm up Walking from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down	12 wks	Plasma (T0) at baseline (T1) at 12 wks	**Within group differences:** T0 vs T1↑; 540.7 ± 289.1[380.6 to 700.8] vs 1120.0 ± 209.2 [999.2 to 1241.0] pg/mL (p<0.001); Cohen's d=3246	ES_{G1}= 2.325
Aguiar et al., 2014 NRUCT	OAk (Sx+Rx) N=27 (81.5%) Female: NA (81.8%) Male: NA (18.2%) 58.8 ± 6.4	1/ Other: Flexibility + strength 3x/week, 80min/day Supervised Week 1-4: 60% of max. load Week 5-8: 70% max. load Week 9-12: full weight determined by 10-MR test	12 wks	Serum (T0) at baseline (T1) at 12 wks (change after training)	**Within group differences:** T0 vs T1: ND[2][4]; 1275.32 [119.53-2329.49] vs 1257.97 [7.46 – 2002.58] pg/mL[5][16]	$ES_{T1\text{-}T0}$= -0.033
sTNFR1 Acute effects						
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic 3x/week 5min warm up Walking	12 wks	Plasma (T0) at baseline: (T00) pre-acute EX (T01) post-acute	**Within group differences:** T0: T00 vs T01 vs T02[4] 538.46 [163.46-1028.85] vs 1278.85 [413.46-1971.15] vs 1115.38 [461.54-1961.54] pg/mL[5] T00 vs T01↑ (p<0.001)	

		from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down		EX (T02) 30' post-acute EX (T1) at 12 weeks: (T10) pre-acute EX (T11) post-acute EX (T12) 30' post-acute EX	T00 vs T02↑ (p<0.001) T01 vs T02: ND[2] <u>T1:</u> T10 vs T11 vs T12[4] 1125 [788.46-1519.23] vs 951.92 [375-1375] vs 721.15 [153.85-1307.69] pg/mL[5] T10 vs T12↓ (p<0.01) T11 vs T12↓ (p<0.05) <u>T0 vs T1:</u> T01 vs T11↓ (p<0.05) T02 vs T12↓ (p<0.01)	
sTNFR2 Basal effects						
Nicklas et al., 2004 RCT	OAk (Rx) N=316 (79.7%) Female[16]: 71.7% (NA)[1] Male[16]: 28.9% (NA)[1] (G1) 69 ± 6[6] (G2) 68 ± 7[6] (G3) 68 ± 5[6] (G4) 69 ± 6[6]	4/ (G1) Aerobic + strength (G2) Diet + aerobic + strength (G3) Diet (G4) Control: healthy lifestyle 1h, 3x/week: Aerobic (walking 15 min, 50-75%HRR), resistance training (2x12 repetitions, 15 min), aerobic (15 min), cooling down (15 min)	18 mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo	**<u>Between group differences: G1 vs G2 vs G3 vs G4</u>** T0: ND: 2760 ± 807 vs 2656 ± 792 vs 2674 ± 842 vs 2850 ± 1127 pg/mL[2] <u>ΔsTNFR2</u> T0 - T1: -148 ± 409 vs -78 ± 427 vs -53 ± 547 vs -59 ± 915 pg/mL[2] T0 - T2: 24 ± 514 vs -61 ± 460 vs 38 ± 665 vs 38 ± 561 pg/mL[2] G1: ND (p=0.08) G3: ND (p=0.23)	
Simao et al., 2012 RCT	OAk (Sx+Rx) N=35 (91.4%) Female: NA (87.5%) Male: NA (12.5%) (G1) 75 ± 7.4 (G2) 69 ± 3.7 (G3) 71 ± 5.3	3/ (G1) Strength (squat on vibration platform) (G2) Strength (squat) (G3) Control: no change of lifestyle 3x/week Volume of squat training was increased by increasing the time and number of sets and reducing rest time 10 min warm up on a bike at 70%HRmax	12 wks	Plasma (T0) at baseline (T1) at 12 wks	**<u>Between group differences G1 vs G2 vs G3:</u>** <u>T0:</u> 4944.0 «3819-5862» vs 4141.0 «3329 - 4993» vs 3568.0 «3319 - 5002» pg/mL; (p=0.20) <u>T1:</u> 3987.0 «2964 - 5067» vs 3650.0 «2949 - 4719» vs 4673.0 «3266 - 5371» pg/mL **<u>ΔPOST-hoc between:</u>** G2 vs G1: ND: p>0.05 G3 vs G1↓: p<0.01 G3 vs G2: ND: p>0.05	
					<u>Within group differences ΔT0 vs T1</u> [13]**:** G1↓: -996.5 «-1750 to 147.3» pg/mL, (p=0.005) G2: ND: -497.7«-1351 to 2219» pg/mL, (p=0.38) G3: ND: 35.4 «-1206 to 2104» pg/mL ,(p=0.58)	
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic 3x/week 5min warm up Walking from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down	12 wks	Plasma (T0) at baseline (T1) at 12 wks	**<u>Within group differences:</u>** T0 vs T1↓; 4542.8 ± 1688 [3608.0 to 5478.0] vs 3177.5 ± 1050.0 [2596.0 to 3759.0] pg/mL, p<0.001); Cohen's d=1373	ES_{G1}= -0.997
Aguiar et al., 2014 NRUCT	OAk (Sx+Rx) N=27 (81.5%) Female: NA (81.8%) Male: NA (18.2%) 58.8 ± 6.4	1/ Other: Flexibility + strength 3x/week, 80min/day Supervised Week 1-4: 60% of max. load Week 5-8: 70% max. load Week 9-12: full weight determined by 10-MR test	12 wks	Serum (T0) at baseline (T1) at 12 wks (change after training)	**<u>Within group differences:</u>** T0 vs T1: ND[2][4]; 4431.81 [1909.77-6489.78] vs 4436.81 [1640.90 – 6589.61] pg/mL[5][12]	ES_{T1-T0}= 0.004
sTNFR2 Acute effects						
Gomes et al., 2012 NRUCT	OAk (Sx+Rx) N=15 (100%) Female: 100% (100%) 67 ± 4	1/ Aerobic 3x/week 5min warm up Walking from 30 min (week 1) to 55 min (week 12) from 70% HRmax to 80% HRmax 5 min cool-down	12 wks	Plasma (T0) at baseline: (T00) pre-acute EX (T01) post-acute EX (T02) 30' post-acute EX (T1) at 12 wks: (T10) pre-acute EX (T11) post-acute EX (T12) 30' post-acute EX	**<u>Within group differences:</u>** <u>T0:</u> T00 vs T01 vs T02[4] 4562.25 [2795.18-7967.87] vs 3020.08 [1574.30-4722.89] vs 2923.69 [1542.17-5076.31] pg/mL[5] T00 vs T01↓ (p<0.001) T00 vs T02↓ (p<0.001) T01 vs T02: ND[2] <u>T1:</u> T10 vs T11 vs T12[4] 3180.72 [1863.45-5172.69] vs 2795.18 [1156.63-4755.02] vs 2602.41 [1124.50- 4176.71] pg/mL[5] T10 vs T12↓ (p<0.05) T11 vs T12: ND[2]	
Leptin Basal effects						
Miller et al., 2004 RCT	OAk (Sx) N= 309 (97.78%) Female[16]: 73.11% (NA) Male[16]: 26.89% (NA) (G1) 69.1 ± 6.5 (G2) 68.7 ± 6.2 (G3) 68.7 ±6.7 (G4) 67.8 ±6.5	4/ (G1) Exercise (aerobic + strength) (G2) Healthy lifestyle (G3) Diet + exercise (aerobic + strength) (G4) Dietary weight loss	18mo	Serum (T0) at baseline (T1) at 6 mo (T2) at 18 mo	**<u>Within group: T0 vs T1 vs T2</u>** 31.7 ± 19.0 vs 32.0 ± 21.5 vs 29.9 ± 23.0 ng/mL[2] No main exercise effect	

		Exercise content: 60 min, 3x/week 5 min warm-up, 15 min aerobic exercises (50-85% HRR), 20 min strength exercises, 15 min aerobic exercises (50-85% HRR), 5 min cool-down phase				
BDNF Basal effects						
Simao et al., 2019 RCT	OAk (Sx+Rx) N= 15 Female: 100% (100%) (G1) 75 (68.5-81.5) yrs (G2) 71 (67.7-74.3) yrs	2/ (G1) Strength+ whole body vibration + squat exercises (G2) Strength 3x/week 10 min warm-up on cycle at 70% predicted HRmax Intensity of squats was increased by increasing the number of repetitions (6x20s to 8x40s) and reducing resting time (40-25s)	12 wks	Plasma (T0) prior to the intervention 24h after intervention period (T1) at 12 wks	**Between group differences: G1 vs G2** T0: ND: 4778 [2952.4-6603.7] vs 3043 [1623.4-4462.6] pg/mL, (p=0.06) **Delta analysis (pretest-posttest)** G1: 122.1 [13] ± (741.94) [5] pg/mL [2] G2: -2037 [13] ± (612.9) [5] pg/mL [2] G1 ↑ vs G2 ($p \leq 0.05$; effect size: 1.1)	
Gomes et al., 2014 NRUCT	OAk (Sx+Rx) N=16 (100%) Female: 100% (100%) 67 ± 4.41 yrs	1/ Aerobic 3x/week walk training (aquatic and land), 30 min at 70% HR max	12 wks	Plasma (T0) at baseline (T1) at 12 weeks	**Within group differences :** T0 vs T1↑; 8343± 3690 vs 14027 ± 4361 pg/mL, ($p<0.001$)	ES= 1.412
Liu et al., 2019 RCT	OAk (Sx + Rx) N= 140 (77.14%) Female: 76.85% (NA) Male: 23.15% (NA) (G1) 40-70 yrs (G2) 40-68 yrs (G3) 40-70 yrs (G4) 40-70 yrs	4/ (G1) Other: Tai Chi (G2) Other: Baduanjin (G3) Aerobic: Cycling (70-75% max HR) (G4) Control: basic health education 1x/week (G1)+(G2) 5x/week 60 min: 10 min warm-up, 30 min exercise (70-75% max HR), 10 min breathing techniques, 10 min relaxation Under supervision	12 wks	Serum (T0) at baseline (1week before intervention) (T1) after 12wks (within 1 week after finishing intervention)	**Between group differences:** G1 vs G2 vs G3 vs G4 T0: ND: 50.8 (3.8 -173.0) vs 45.4 12.5 – 134.5) vs 31.3 (1.6 – 497.2) vs 54.9 (22.4 – 389.9), (p=0.32) T1-T0: ND: 3.0 ± 42.3 vs 14.6 ± 60.2 vs 1.1 ± 101.5 vs -14.0 ± 50.0, (p= 0.46) **ΔPost-hoc between** G1 vs G4 T1-T0: ND: p= 0.90 G2 vs G4 T1-T0: ND: p= 0.51 G3 vs G4 T1-T0: ND: p= 0.92 G1 vs G2 T1-T0: ND: p= 0.99 G1 vs G3 T1-T0: ND: p= 1.00 G2 vs G3 T1-T0: ND: p= 0.99	$ES_{G1\text{-}G4}$= -0.370 $ES_{G2\text{-}G4}$= -0.512 $ES_{G1\text{-}G4}$= -0.185
BDNF Acute effects						
Gomes et al., 2014 NRUCT	OAk (Sx+Rx) N=16 (100%) Female: 100% (100%) 67 ± 4.41 yrs	1/ Aerobic 2 min warming up walking on treadmill at 1mph 18 min walking on treadmill at 2mph	12 wks	Plasma (T0) at baseline: (T00) pre-acute EX (T01) post-acute EX (T02) 30' post-acute EX (T1) at 12 wks: (T10) pre-acute EX (T11) post-acute EX (T12) 30' post-acute EX	**Within group differences:** T0: T00 vs T01 vs T02 7.693 ± 4.454 vs 12.242 ± 3.806 vs 11.190 ± 3.847 pg/mL T00 vs T01↑ ($p<.0001$) T00 vs T02↑ ($p<0.001$) T1: ND[2][4][18]	$ES_{T01\text{-}T00}$= 1.101 $ES_{T02\text{-}T00}$= 0.843

BDNF: Brain Derived Neurotrophic Factor; **CRP**= C-reactive Protein; **EX**= exercise; **(G)**= group; **IL**= Interleukin; **IL-6sR**=soluble interleukin 6 receptor; **info & rec**= information and recommandations; **mo**=mon Difference; **OAk**=Osteoarthritis knee; **Rx**=radiographic; **sTNFR1**= soluble Tumor Necrosis Factor-α Receptor 1; **sTNFR2**= soluble Tumor Necrosis Factor-α Receptor 2; **Sx**=symptomatic; **TGF-1β**= Transformin **α**=Tumor Necrosis Factor-α; **wks**=weeks; ; **WL**= weight loss; **LE OA**: lower extremities (knee, hip, lower back, ankle) osteoarthritis; **OAh**: hip osteoarthritis; [1]Based on available samples at baseline; [2] p valu visit, gender, baseline BMI, baseline biomarker value; [4] no data reported; [5] results based on graph measurement using GetData Graph Digitizer; [6] range: group with lowest mean age vs group with high sensitivity C-Reactive Protein; [8] interpretation of graphs and text; [9] adjusted for baseline BMI, sex, baseline values(significance level set at .025); [10] significance level set at .008; [11] no graphs; [12]only levels below minimum detectable concentration; [13] p values/concentrations obtained from author; [14] mean; [15] adjusted for baseline values, age, gender and BMI; [16]obese; [17]intention to treat analysis [19]median; [20] adjusted for baseline values baseline BMI and gender; [21] adjusted for age and baseline BMI; ↑ = significant increase; ↓= significant decrease; SD: significant difference; i.d.a.: insufficient dat (before–after); **1x=** one session; mean± SD; mean± (SE); median (minimum - maximum); median «interquartil range»; mean[minimum - maximum]; mean ± SD[95% CI: ...to...]; mean[95% CI: ...to...]

Table 4:
Risk of Bias. 4A) Risk of bias in RCTs. 4B) Risk of bias in NR(U)CTs



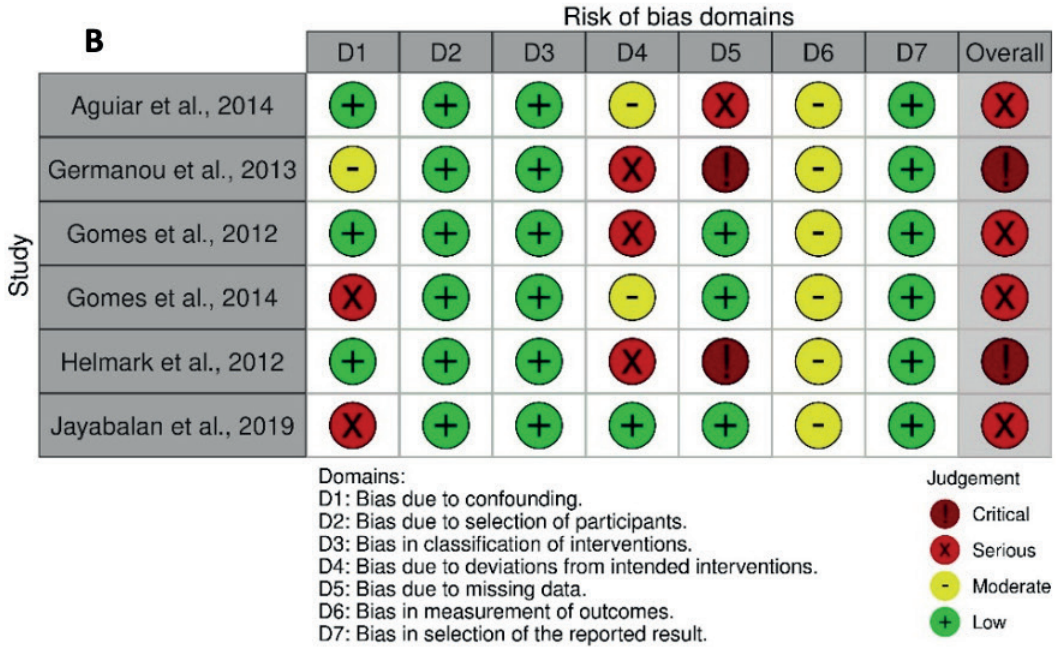


Table 5:
Schematic summary of the findings per biomarker

Biomarkers with a pro-inflammatory character:			
Biomarker	**BE/AE**	**Type analysis**	**Effect exercise therapy**
CRP	BE	*Meta-analysis*	↓ (Samut et al.,2015; Nicklas et al.,2004)
		Training vs. control group	↔ (Kim et al.,2021)
		Within training group	↔ (Germanou et al., 2013), ↔ (Beavers et al., 2015)
	AE	*Within training group*	↔ (Germanou et al.,2013)
CRPM	BE	*Within training group*	↔ (Loeser et al., 2017)
IL-1β	BE	*Within training group*	↔ (Alkatan et al., 2016; Armagan et al.,2012) ↓° (Zhao et al., 2019; Messier et al., 2000)
IL-5	BE	*Within training group*	↔ (Alkatan et al., 2016)
IL-6	BE	*Meta-analysis*	↔ (Samut et al., 2015; Nicklas et al.,2004)
		Training vs. control group	↔ (Kim et al., 2021)
		Within training group	↔ (Messier et al;,2013), ↔ (Germanou et al., 2013 ; Gomes et al.,2012), ↓ (Alkatan et al.,2016), ↓ (Aguiar et al.,2015)
IL-6sR	BE	*Within training group*	↔ (Nicklas et al.,2004)
IL-7	BE	*Within training group*	↔ (Alkatan et al., 2016)
IL-8	BE	*Within training group*	↔ (Alkatan et al.,2016)
	AE	*Training vs. control group*	↔° (Helmark et al.,2010)
		Within training group	↑°(Helmark et al.,2010)
IL-12	BE	*Within training group*	↔ (Alkatan et al.,2016)

TNF-α	BE	*Meta-analysis*	↓ (Samut et al.,2015; Nicklas et al.,2004)
		Training vs. control group	↔ (Kim et al.,2021)
		Within training group	↓° (Zhao et al., 2019), ↔ (Gomes et al., 2012 ; Aguiar et al.,2015), ↔ (Alkatan et al., 2016)
	AE	*Training vs. control group*	↔° (Helmark et al., 2010)
		Within training group	↑° (Helmark et al., 2010), ↔ (Jayabalan et al., 2019), ↔ (Gomes et al.,2012)
Leptin	BE	*Within training group*	↔ (Miller et al., 2004)

Biomarkers with an anti-inflammatory character:			
Biomarker	**BE/AE**	**Type analysis**	**Effect exercise therapy**
IL-2	**BE**	*Within training group*	↔ (Alkatan et al., 2016)
IL-4	**BE**	*Within training group*	↔ (Alkatan et al., 2016)
IL-6	**AE**	*Training vs. control group*	↔°(Helmark et al., 2010)
		Within training group	↑(Germanou et al., 2013), ↑°(Helmark et al., 2010), ↔° (Helmark et al., 2012), ↔ (Gomes et al., 2012)
IL-10	**BE**	*Within training group*	↔ (Alkatan et al., 2016), ↑° (Zhao et al., 2019)
	AE	*Training vs. control group*	↔° (Helmark et al., 2010)
		Within training group	↑° (Helmark et al., 2010)
IL-13	**BE**	*Within training group*	↔ (Alkatan et al., 2016)
sTNFR1	**BE**	*Meta-analysis*	↔ (Nicklas et al., 2004; Simao et al., 2012)
		Within training group	↔ (Simao et al., 2012), ↑(Gomes et al., 2012), ↔(Aguiar et al., 2015)
	AE	*Within training group*	↑(Gomes et al., 2012), ↓(Gomes et al., 2012)

sTNFR2	**BE**	*Meta-analysis*	**↔ (Nicklas et al., 2004; Simao et al., 2012)**
		Within training group	**↔(Simao et al.,2012)**, ↓(Gomes et al.,2012), ↔(Aguiar et al.,2015)
	AE	*Within training group*	↓(Gomes et al.,2012)
BDNF			
Biomarker	**BE/AE**	**Type analysis**	**Effect exercise therapy**
BDNF	**BE**	*Training vs. control group*	**↔(Liu et al., 2019)**
		Within training group	↑(Gomes et al., 2014)
	AE	*Within training group*	↑(Gomes et al., 2014), ↔ (Gomes et al., 2014)

'↑' indicates an increase , '↓' indicates a decrease, '↔' indicates no change, arrow written in bold indicates evidence based on RCT, arrow in grey indicates evidence based on NR(U)CT

BE : basal effect ; AE : acute effect A: aerobics; S: strength training; IL: interleukin, sTNFR: soluble tumor necrosis factor receptor, BDNF: brain derived neurotrophic factor, TNF: tumor necrosis factor, CRP: C-reactive protein