A systematic literature review on the effects of exercise on human Toll-like receptor expression

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ABSTRACT

Background

Toll-like receptors (TLRs) are a family of transmembrane pattern recognition receptors that are mainly expressed on immune cells. Recognition of various exogenous and endogenous molecular patterns activates the TLR signalling cascade, which orchestrates an inflammatory immune response. Dysfunctional immune responses, including aberrant TLR signalling, are increasingly implicated in the associations between sedentarism, chronic low-grade systemic inflammation and various non-communicable diseases. Conversely, exercise exerts anti-inflammatory effects, which could be conferred through its immunomodulatory properties, potentially affecting TLRs. This study aims to systematically review the effects of exercise on human TLR expression.

Method

A systematic literature search of Pubmed, Embase, The Cochrane Library and SPORTDiscus for articles addressing the impact of exercise (as isolated intervention) on TLRs in humans was conducted, ending in February 2020.

Results

A total of 66 articles were included. The publications were categorised according to exercise modality and duration: acute resistance exercise (4 studies), acute aerobic exercise (26 studies), resistance training program (9 studies), aerobic training program (16 studies), combined (i.e. resistance and aerobic) training program (8 studies) and chronic exercise not otherwise classifiable (9 studies). Five articles investigated more than one of the aforementioned exercise categories.

Several trends could be discerned with regard to the TLR response in the different exercise categories. Acute resistance exercise seemed to elicit TLR upregulation, whereas acute aerobic exercise had less activating potential with the majority of responses being neutral or, especially in healthy participants, downregulatory. Chronic resistance and combined exercise programs predominantly resulted in unaltered or decreased TLR levels. In the chronic aerobic exercise category, mixed effects were observed, but the majority of measurements demonstrated unchanged TLR expression.

Conclusion

Currently published research supports an interplay between exercise and TLR signalling, which seems to depend on the characteristics of the exercise. However, there was large heterogeneity in the study designs and methodologies. Therefore, additional research is required to further corroborate these findings, to define its pathophysiological implications and to elucidate the mechanism(s) linking exercise to TLR signalling.

Keywords: Exercise, Toll-like receptor, immunity, inflammation, systematic review

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INTRODUCTION

Low-grade chronic inflammation has been implicated in the pathogenesis of numerous chronic diseases, including atherosclerosis, heart failure, diabetes mellitus, obstructive pulmonary diseases, rheumatoid arthritis, dementia and particular types of cancer.(9, 27, 38, 68, 69, 115) Physical inactivity seems to contribute significantly to the development of a state of systemic inflammation, which has led to the paradigm of 'inflamm-inactivity'.(57) Conversely, physical activity (*i.e.* exercise) elicits anti-inflammatory adaptations, which would confer a protective effect against chronic inflammation-associated diseases.(22, 68, 129, 130) However, the mechanisms underlying the anti-inflammatory effects of exercise are not fully understood.(35) It is known that physical exercise can modulate an array of immunological responses.(9) The possibility that exercise mediates these anti-inflammatory effects by affecting Toll-like receptor (TLR) signalling has gained increasing attention in the last decade.(9) Nevertheless, the literature still lacks clarity.

Toll-like receptors

TLRs are a family of evolutionarily conserved transmembrane glycoprotein receptors.(17, 49) To date, 13 members of the TLR family have been identified in mice, and 10 (TLR1-10) in humans.(69) TLRs are widely distributed and expressed in various cell types and tissues, but primarily in/on immune cells.(4, 9, 51, 118, 159, 211) They recognise a variety of exogenous and endogenous signals. More specifically, TLRs respond to distinct molecular patterns and are therefore designated as pattern recognition receptors (PRRs). The recognised molecular motifs can be divided into pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs are invariant molecular structures shared by a large spectrum of microbial pathogens. As such, TLRs play an important role in the defence against Gram-negative and Gram-positive bacteria, DNA and RNA viruses, fungi and protozoa.(17) DAMPs, on the other hand, are endogenous signals released by stressed or injured cells. In physiological conditions, DAMPs are hidden from recognition by the host immune system.(154) The known ligands for each of the TLRs are summarised in Supplementary Table 1.

The conserved nature of the TLRs is related to their central role in both innate and adaptive immunity.(43) TLR activation typically generates a pro-inflammatory environment, potentially leading to the aforementioned disease states.(34, 38, 43, 65, 118, 153) Therefore, TLRs are a focus of investigation in the associations between sedentarism, inflammation and disease.(39)

An overview of the TLR signalling pathways and their differential expression in/on monocyte and dendritic cell subtypes can be found in the Supplementary Material.

Exercise and Toll-like receptors

It has been hypothesised that exercise exerts its anti-inflammatory effects through modulation of TLR signalling. Several viable mechanisms exist to substantiate this proposed relationship. Especially serum factors whose kinetics are influenced by exercise have been put forward as candidates to explain such relationship. These include circulatory cytokines, translocated lipopolysaccharide (LPS) from the gastrointestinal tract, fatty acids, hormones (glucocorticoids, catecholamines, insulin-like growth factor 1 and growth hormone) and heat-shock proteins (HSPs).(128) Also DAMPs, muscle derived microRNAs (miRNAs) (potentially DAMP-induced), autophagy-related proteins, oxidative stress and acidosis have been suggested as mediators.(17, 46, 65, 119, 128, 174, 190) A commonly cited mechanism of action is tolerance or cross-tolerance by (low-dose) exposure.(94, 141, 153, 174) More recently, soluble forms of some TLRs have been identified in various body fluids. Consequently, it was suggested that TLR downregulation could also be mediated by receptor shedding.(39, 43, 68, 98, 216)

Aims of this systematic review

The concept that exercise modulates TLR signalling has gained attention in the last decade. However, conflicting results have been reported, suggesting that the modality and duration of the physical stimulus may be a strong determinant of the outcome. Previous reviews on the relationship between exercise and TLRs were limited to patients with the metabolic syndrome(145), not systematic in design(39, 68), not focused on TLRs (but on inflammatory markers in general)(67, 68) or only concentrated on specific TLRs(27). The aim of this review was to present a systematic overview of the literature on the effect of exercise on TLRs to date. In addition, special attention is paid to the impact of the health status and age of the subjects, and to concurrent alterations in leukocyte populations, which predominantly harbour TLRs.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(123)

Search strategy and selection criteria

We searched the electronic databases Pubmed, Embase, The Cochrane Library and SPORTDiscus for articles addressing the impact of exercise on Toll-like receptors. Electronic searches were conducted from inception to 21 February 2020. There were no restrictions with regard to publication year unless stated otherwise. Pubmed was searched with the following Medical Subject Heading (MeSH) terms: ("Toll-Like Receptors"[Mesh]) AND "Exercise"[Mesh]. In order not to disregard very recent articles without MeSH indexation, we also ran a query with free-text fields, which was restricted to articles published since 1 January 2019: ("exercise"[MeSH Terms] OR "exercise"[All Fields]) AND ("toll-like receptors"[MeSH Terms] OR ("toll-like"[All Fields] AND "receptors"[All Fields]) OR "toll-like receptors"[All Fields] OR ("toll"[All Fields] AND "like"[All Fields] AND "receptor"[All Fields])). For Embase, we used the query: ('exercise'/exp OR exercise) AND ('toll like receptor'/exp OR 'toll like receptor'). The "/exp" indicates that this is an "explosion" in Emtree and that related terms are also included. SPORTDiscus was consulted with the query: (exercise or physical activity) AND toll-like receptors. For The Cochrane Library the following keywords were used: exercise in Title Abstract Keyword AND toll-like receptor in Title Abstract Keyword. In addition, references from previous articles were hand-searched.

Studies describing the (direct) impact of exercise (without restriction on modality, intensity or load) on Toll-like receptors (both gene and protein level) in human subjects were eligible for inclusion. There were no predefined criteria with regard to age, sex and health status of the study subjects. Both observational and interventional designs were accepted.

Animal studies were excluded. This review was restricted to articles written in English or Dutch. Results published in abstract form were not included as this prohibits adequate evaluation of study quality and bias. Commentaries, letters to the editor, editorials and project proposals were also excluded. Studies containing insufficient information, or with no full-text of the manuscript available were to be excluded if no response was received after contacting the authors through e-mail.

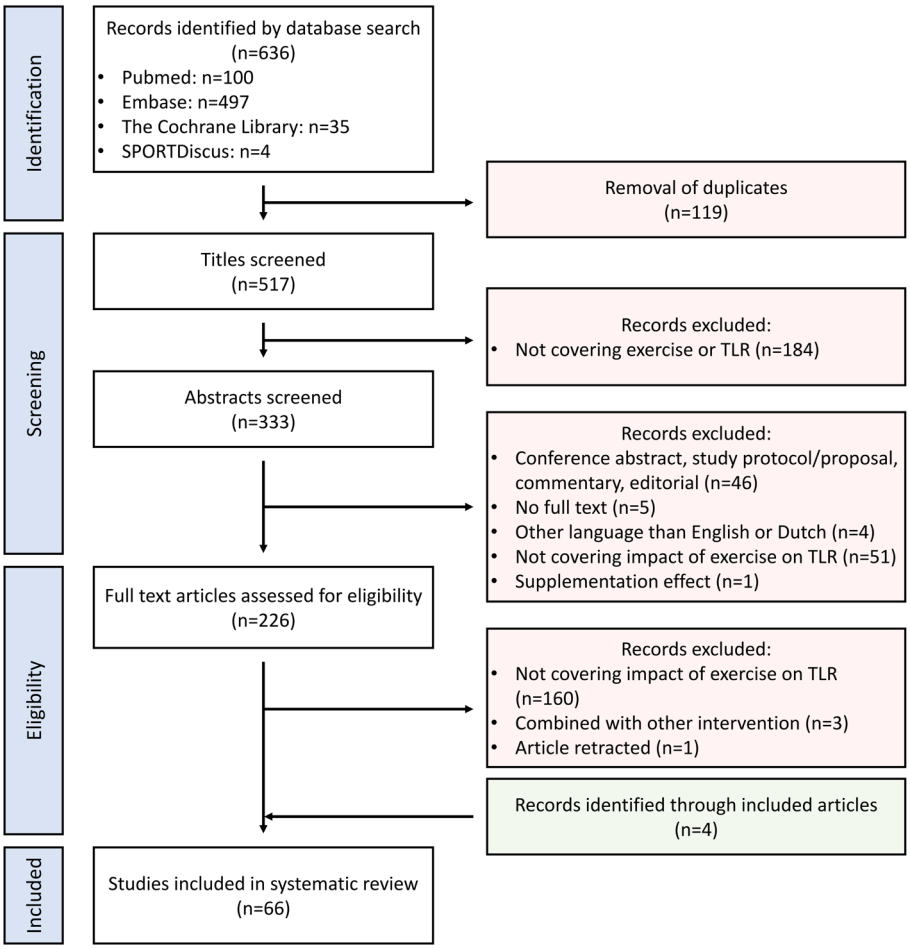
Study selection and data extraction

The searches were exported to EndNote X9. Duplicates were removed. First, KF assessed titles and abstracts for eligibility. Next, two independent researchers (KF and MB) checked the full text of the articles that were considered relevant in a first phase against the predefined inclusion and exclusion criteria.

A data extraction spreadsheet was created. KF extracted information on study design, study population, exercise characteristics (modality, intensity, duration), specimen collection, analytical technique and outcomes.

Simultaneously to the data extraction, the study quality and the risk of bias were assessed. Disagreements between both researchers regarding study inclusion, and any ambiguities regarding data extraction, and quality and risk of bias assessment were discussed within the wider team (KF, MB, HH and PJG).

Figure 1 | Flow diagram of the study selection process.



RESULTS

Literature search

Figure 1 summarises the study selection process. The search of the 4 electronic databases identified 636 articles with 517 articles remaining after removal of duplicates. Of these, 184 articles were excluded after screening of the titles and 107 after screening of the abstract. The main reason for exclusion was the subject matter (*i.e.* not investigating the impact of exercise on TLRs), but also articles that combined exercise with another intervention (hereby obscuring the exercise impact) were removed at this stage. Forty-six articles were excluded based on article type (*i.e.* conference abstract, project protocol or proposal, commentary or editorial). Of the 226 retrieved articles, 165 were excluded after full text review. Subject matter not fitting the scope of this review and combined interventions were the main reasons. Eventually, 62 articles were eligible for inclusion in this review. Through detailed review of the reference lists of the included articles, an additional 4 references were found eligible and were included.(35, 108, 112, 189) For scientific substantiation, an additional 150 trials were consulted without complying with the predefined inclusion and exclusion criteria.

Characteristics of the included trials

The characteristics of the included trials are presented in Supplementary Tables 2-7. The majority of studies (55%) was published in the time period 2015-2020. Sixty-two percent of the articles studied healthy subjects (we considered overweight and obesity to be a pathological state). Regarding the exercise modality, 40 (58%) articles studied the effects of endurance exercise, 13 (19%) the effect of resistance exercise and the remainder (8 studies, 12%) evaluated combined forms of exercise. Twelve percent of the exercise forms were not classifiable. The majority of trials (55%) evaluated the effects of chronic exercise training, 41% focused on the impact of an acute exercise bout and 5% combined the effects of acute and chronic exercise.

Eight trials did not mention the sex distribution of the subjects studied. (54, 115, 119, 126, 150, 154, 155, 180) Among the 12 randomised controlled trials (RCTs), the main issues regarding bias were lack of blinding of participants and study personnel, and lack of blinding of outcome assessment.(5, 40, 51, 52, 94, 119, 124, 142, 154, 155, 172, 174) Information regarding the allocation process was not present in 83% of the studies.

Impact of exercise on Toll-like receptors

To study the impact of exercise on TLRs, we have categorised the exercise protocols according to their modality (resistance versus endurance) and duration (acute versus chronic). We acknowledge that the dichotomisation of exercise into resistance and endurance effort is very artificial and unphysiological, however, the heterogeneity of the study protocols did not allow for a valuable alternative.(56) Chronic exercise (exercise training) can be defined as a repeated amount of exercise bouts during a short or long period of time, while acute exercise can be defined as a single bout of exercise.(165) The effects of chronic exercise should be evaluated after sufficient exercise abstinence to avoid interference from delayed acute effects. The findings per exercise category are summarised in Figure 2.

For each exercise category, we first discuss the findings in healthy subjects, and subsequently in participants with a pathological condition. We conclude each section with data on the impact of age and physical activity status.

Acute resistance exercise

Only four studies investigated the effect of a bout of resistance exercise on Toll-like receptors.(51, 52, 58, 116) All were performed in apparently healthy subjects. Contrary to the previous review by Cavalcante *et al.*, we chose to classify the staircase running exercise of Millard *et al.* as an acute aerobic stimulus.(27, 121)

In 2003, Flynn *et al.* subjected elderly resistive-trained women to a resistance training program and evaluated the response to a subsequent acute bout. No difference in TLR4 mRNA was noted in response to the exercise bout, although the trained group did show lower resting TLR4 mRNA levels compared to a sedentary control group at the end of the program.(58) One year later, McFarlin *et al.* compared the response of trained and untrained elderly women to a series of upper and lower body resistance exercises. The untrained group showed higher levels of TLR4 expression on monocytes at baseline, but no exercise-induced alterations in TLR4 (both at gene and cell surface level) were observed (in contrast to the interpretation of Cavalcante *et al.* of these study results).(27) *Ex vivo* LPS-stimulation of the blood samples did show increased cytokine production in the post-exercise samples.(116) Fernandez-Gonzalo *et al.* first studied a group of healthy young and moderately active male students. An eccentric exercise bout induced increased gene expression and protein levels of TLR4 in peripheral blood mononuclear cells (PBMCs). Also other proteins of the TLR signalling pathway (*i.a.* myeloid differentiation primary response gene 88 (MyD88), TNFR-associated factor (TRAF) 6, extracellular signal-regulated protein kinase (ERK) 1/2, TIR-domain-containing adaptor protein-inducing interferon-β (TRIF)) and tumor necrosis factor alpha (TNF-α) were upregulated. Next, he repeated the exercise bout after half of the students had completed a 6-week eccentric training program. Remarkably, the trained students showed decreased protein levels of TLR4 after the second bout and stable levels of pathway proteins and TNF-α, whereas the response of the control group was identical to the first bout.(51) They later corroborated these findings in female students where TLR4 protein levels were elevated after the first bout and remained stable after the second bout. It is worth mentioning that in both studies the TLR4 mRNA remained elevated with a different response at protein level as discussed above.(52)

Acute aerobic exercise

Twenty-three articles evaluated the effects of acute aerobic exercise. Study subjects varied from young endurance-trained athletes and professional soccer players to sedentary and diseased patients.(22, 69) No elderly were included in any of the trials. There was large variation between studies in every aspect of the aerobic stimulus. The exercise intensity was between moderate (50% VO_2max) and maximal.(12) Exercise duration varied from very brief (68.6 seconds) to long-lasting (263 minutes).(121, 129) Lastly, environmental conditions ranged from cold (1°C) outdoor conditions to an environmental chamber with room temperature of 37°C and relative humidity of 25%.(2)

One study evaluated TLR expression in (vastus lateralis) muscle tissue, the other study groups focused on venous blood samples. Monocytes were the most frequently studied cell fraction within the blood samples (8/23). The most commonly used analysis methods were PCR-based techniques to evaluate gene expression (11/23 studies) and flow cytometry (9/23 studies). Western blot was less frequently applied (4/23). Only one study simultaneously evaluated the TLR gene and protein level.(129)

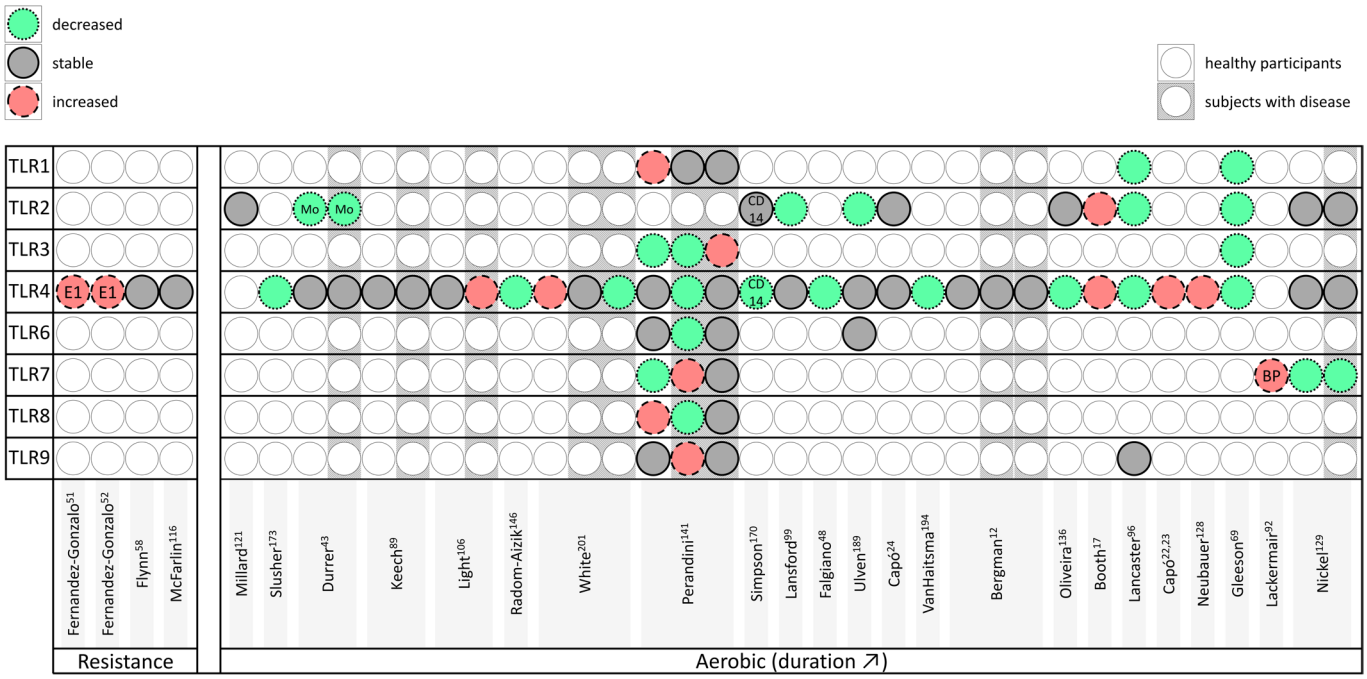
In healthy participants, the majority of studies showed downregulated (19/45; 42%) or stable (18/45; 40%) levels of TLR gene or protein expression, with only a minority recording increased levels (8/45; 18%). Studies that evaluated different TLR family members demonstrated that they can react differently to the same exercise stimulus. The predominant response(s) of the different TLRs was decrease for TLR1 (2/3), TLR2 (5/11), TLR3 (2/2) and TLR7 (2/3), stable levels for TLR2 (5/11), TLR4 (9/21), TLR6 (2/2) and TLR9 (2/2), and increase for TLR8 (1/1).

Five studies with an initial response of TLR to exercise performed a re-evaluation after several hours of recovery and all demonstrated normalisation to baseline levels (after 4-48 hours). Only one subgroup in the study of VanHaitsma *et al.*, that was subjected to cycling in a hot environmental chamber, showed persistent decrease in TLR4 expression after 48 hours.(194) Five studies simultaneously determined the levels of several TLR signalling pathway molecules.(24, 48, 128, 141) In three of these studies, the response of these molecules corresponded to the TLR response. The results of *ex vivo* stimulation assays, although difficult to interpret for reasons explained in the discussion section on the methodological approach, were in agreement with the TLR response in 4 out of 6 studies. Cytokine levels were assessed in 11 studies, with responses matching to TLR changes in 7 studies.

As already discussed in the introduction, we know that certain pathological conditions are associated with an inflammatory state. This inflammatory milieu at baseline could affect the TLR response to exercise. In addition to healthy participants, seven studies also included one or more patient groups. The majority of observations showed unchanged TLR levels (14/25; 56%), followed by decreased (7/25; 28%) and increased (4/25; 16%) levels. In one of the two studies that simultaneously assessed the response of the TLR signalling pathway molecules, the response could be considered congruent to the TLR response.(12, 141) Durrer *et al.* performed

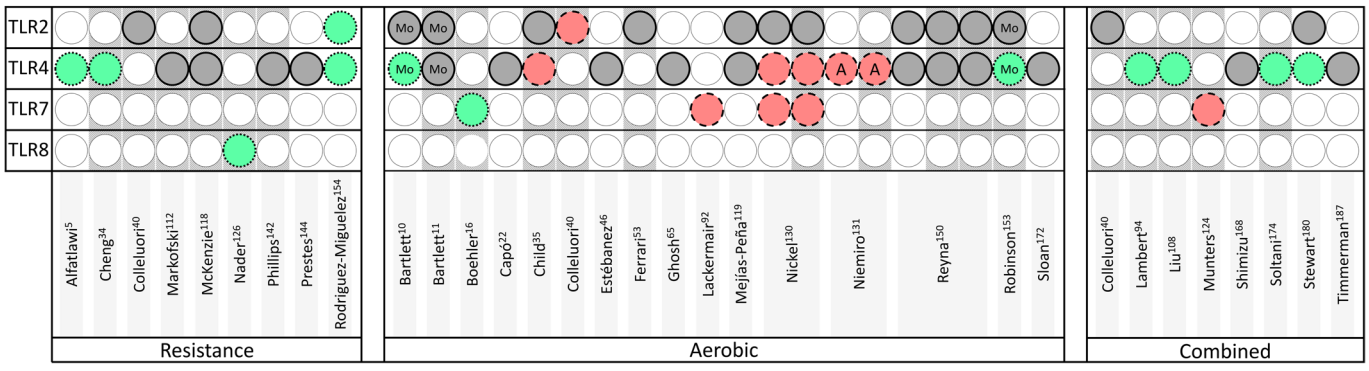
Figure 2 | Impact of exercise on individual TLR receptors according to exercise category.

A) Acute exercise bout.



The X-axis denotes exercise modality, first author and corresponding reference. Studies examining the impact of acute aerobic exercise were ranked according to duration of the exercise bout from left (short duration) to right (long duration). Responses have been categorised as increased (red colour; dashed outline), stable (grey colour; solid outline) or decreased (green colour; speckled outline). If both gene and protein level were available, only protein expression was considered. In healthy participants, the circles corresponding to the TLR responses are placed on a white background. In subjects with disease, the circles are superimposed on a striped background. E1, only first exercise bout was taken into account. Mo, only monocytes were considered. CD14, response of total $CD14^+$ cells. BP, biphasic response with increase more pronounced than decrease.

B) Exercise training program.



The X-axis denotes exercise modality, first author and corresponding reference. Responses have been categorised as increased (red colour; dashed outline), stable (grey colour; solid outline) or decreased (green colour; speckled outline). If both gene and protein level were available, only protein expression was considered. In healthy participants, the circles corresponding to the TLR responses are placed on a white background. In subjects with disease, the circles are superimposed on a striped background. Mo, only monocytes were considered: CD14+ monocytes (153) or non-classical monocytes (10, 11). A, ambiguous response, interpreted as increase.

ex vivo stimulation of blood cultures of type 2 diabetes patients and noticed lower TNF-α production after exercise, which is in line with findings regarding TLR expression.(43) Cytokine levels were evaluated in 10 studies, and in 5 of them the response was in agreement with the TLR response.

When directly comparing healthy controls and patient groups, 4 out of 6 studies showed identical TLR responses to exercise. In the two studies that showed differences, there were also differences between the different patient groups. One of these studies reported increased TLR expression after exercise in healthy controls, unchanged TLR levels in chronic fatigue syndrome (CFS) patients and decreased levels in multiple sclerosis (MS) patients.(201) Perandini *et al.* compared gene expression in response to exercise of patients with active or inactive systemic lupus erythematosus (SLE) and healthy controls, and although innate and adaptive immunity was downregulated in all groups, differences in the kinetics of the expression changes of the different TLRs were noticed.(141)

Also age and baseline physical activity status could influence the TLR response to exercise. All of the upregulatory responses occurred in young and physically active individuals, although overall, far more stable or downregulatory responses were recorded in these subjects. Only two studies included subjects of middle age, and no elderly were studied in any of the trials. Capó *et al.* found similar results in young and 'senior' athletes.(24) Bergman *et al.* and Nickel *et al.* compared sedentary subjects to athletes and non-elite to elite athletes respectively, and no differences in TLR response to exercise were observed.(12, 129) In the trial of Bergman *et al.*, the predefined intensity level was expressed as a percentage of the VO_2max and thus corrected for the aerobic capacity of the participants.

Two studies were not considered in the aforementioned evaluation due to their particular design. Sureda *et al.* recruited professional divers to perform an immersion to a depth of 50 metres. Stable expression of TLR2 and increased expression of TLR4 and NF-κB were reported, but possible effects of hyperoxia and hyperbaria must be taken into account.(181) Fuller *et al.* subjected the participants to an acute cycling bout, but blood sampling was only performed 16-18 hours later (to assess the impact of a high fat meal). They demonstrated stable levels after 16-18 and 20-22 hours, which could correspond to the recovery of TLR within hours after exercise as mentioned above.(62)

Resistance exercise program

Nine studies assessed the impact of a resistance exercise program. The status of the patient groups varied from healthy to sedentary, obese, frail or even diseased (*e.g.* auto-immune inflammatory myopathy or recovering from a hip fracture). The majority of patients were elderly, with only 2 groups being middle-aged. The duration of the programs ranged from 4 to 26 weeks, all with 2-3 sessions per week. Seven out of nine programs consisted of upper and lower body exercises. The training intensity is difficult to estimate given the differences in number of sets and repetitions.

The tissues subjected to analysis included whole venous blood, serum, peripheral blood cells, PBMC, lymphocytes, vastus lateralis muscle and subcutaneous adipose tissue. The analytical techniques were mainly gene expression based (6/9). In the different studies together, only three receptors (TLR2, TLR4 and TLR8) were evaluated.

Three trials recruited healthy participants to assess the impact of their training program. In total, 4 responses were recorded, of which 3 showed decreased and 1 unchanged TLR levels. Rodriguez-Miguelez *et al.* looked into molecules involved in the TLR signalling pathway, and similar to the TLR response, downregulation was observed.(154) No *ex vivo* stimulation assays were performed. In all three studies, cytokine assays of peripheral blood were in agreement with the TLR response.

Six studies (solely) focused on patients with various pathologies. Of the 7 TLR responses recorded, 5 were stable and 2 downregulated. Four studies simultaneously determined TLR pathway molecule levels, and these were in accordance with the TLR response in 3 of them.(34, 40, 118, 126) Two studies performed *ex vivo* stimulation assays and in both the results were in accordance with the TLR response.(112, 142) Five studies determined cytokine levels, and these were in agreement with the TLR response in two studies.(34, 40, 118, 126, 142)

Insufficient information is available to make any statements regarding the impact of the patient characteristics. The exercise programs were limited to middle-aged or elderly subjects with little physical activity (although five trials did not provide exact information on the baseline physical activity status). As obesity is associated with a state of meta-inflammation, one would expect these patients to have additional 'room for improvement' with regard to TLR lowering. Remarkably, the trials that studied overweight/obese subjects all reported absence of TLR alterations.(40, 112, 142)

In addition to the effects of the resistance exercise program itself, such program can also modulate the effects exerted by acute exercise bouts. As previously mentioned, Fernandez-Gonzalo and colleagues demonstrated that an eccentric exercise program attenuated the TLR-mediated pro-inflammatory response after a bout of eccentric exercise.(51, 52)

Aerobic exercise program

Sixteen studies were included to evaluate the effect of chronic aerobic exercise on TLRs. The study population varied from young sports professionals to sedentary, obese elderly and patients with chronic diseases (myositis, rheumatoid arthritis). The exercise program duration ranged from very brief (2 weeks) to long-lasting (26 weeks). Session load was situated between 2 sessions per week and daily. Again, exercise intensity is difficult to quantify, especially given the fact that most programs gradually increased the intensity throughout their program.

Most studies focused on PBMCs or blood monocytes. Three studies examined vastus lateralis muscle tissue. The use of flow cytometry, Western blot and gene-based techniques were equally distributed. Only TLR2, TLR4 and TLR7 were examined.

In healthy participants, the majority of assessments in 10 studies found no impact of exercise training on TLR expression (10/15; 67%). Four of the evaluations (4/15; 27%) showed TLR upregulation, and in one occasion (1/15; 7%), the TLR level was decreased. Pathway molecules were assessed in 4 studies, with accordance with the TLR response in 3 of them.

Sloan *et al.* evaluated inducible cytokine production in whole blood and found no effect of exercise training, corresponding to the observed TLR response.(172) Regarding *ex vivo* assays, Bartlett *et al.* reported increased monocytic phagocytosis and oxidative burst compared to pre-exercise, while stable TLR2 levels and reduced TLR4 levels were reported.(10) Of the 4 trials that investigated cytokine responses, 3 showed analogous responses to TLR.

In nine studies, one or more patient groups were included. Ten of the 17 responses recorded (10/17; 59%) showed unchanged TLR levels. TLR expression was increased in 5 of the 17 assessments (5/17; 29%) and decreased in two assessments (2/17; 12%). Pathway molecules showed concordance to the TLR response in 2 out of the 3 studies that performed the assessment.(40, 130, 150) Robinson *et al.* assessed inducible cytokine production in whole blood cultures, and found no effect of exercise training, corresponding to the observed TLR response.(153) On the contrary, Bartlett *et al.* reported increased *ex vivo* monocyte phagocytosis with stable levels of TLR2 and TLR4 expression on classical and non-classical monocytes.(11) Regarding the cytokine response, accordance to the TLR response was described in 4 out of 5 studies.(11, 40, 53, 130, 153)

No distinguishable patterns were found regarding the influence of age and health status on the TLR response. Three studies compared lean and obese subjects with a comparable physical activity status and reported similar responses to an aerobic exercise program.(130, 131, 150) Only three studies included non-sedentary subjects and no study included both sedentary and non-sedentary groups. Nickel *et al.* compared non-elite and elite athletes and no significant group differences were reported.(130)

Combined exercise program

Eight studies were considered eligible for the evaluation of combined exercise programs. All of the subjects were physically inactive. Some of the participants suffered from obesity or type 2 diabetes mellitus and one group was diagnosed with inflammatory myopathies. Patient age varied from college-aged to elderly. The shortest program spanned only two weeks, the longest 26 weeks. In the program of 2 weeks, 5 sessions per week were planned, the other programs scheduled 2-3 sessions per week. All of the programs combined aerobic and resistance exercises within the same session, although this was not clearly mentioned in one of the research articles. Three research groups studied the effects on vastus lateralis muscle tissue, the other groups analysed PBMCs or blood monocytes. Three of the 8 studies used flow cytometry, the other studies used gene expression analysis. One study performed mRNA and protein analysis simultaneously.(108) Only TLR2, TLR4 and TR7 were evaluated.

Only three studies investigated the effects of a combined exercise program in healthy subjects. The TLR levels were unchanged in three out of four assessments (TLR2 1/1 and TLR4 2/3), and one time decreased (TLR4 1/3). The result of the *ex vivo* stimulation assay matched the observed TLR alterations in 1 of the 2 studies performing this analysis.(180, 187) No TLR pathway molecules or cytokine values were assessed.

Five studies were conducted in participants with disease. Three downregulatory TLR responses (TLR4 3/3), one stable (TLR2 1/1) and one upregulatory (TLR7 1/1) response were reported. Pathway member alterations were concordant with TLR responses in 2 out of 3 studies (one with downregulatory and one with unaltered responses).(40, 108, 174) No *ex vivo* stimulation assays were performed. With regard to cytokine determination, the response was in accordance with the TLR response in two of the four trials determining the cytokine levels.(40, 94, 108, 124)

As mentioned above, all of the subjects were physically inactive. Therefore, it is unclear if baseline physical activity status influences the TLR response to a combined exercise program. Only two studies included subjects of young age. One study performed the comparison with an elderly group and an identical TLR response was reported.(180) No direct comparisons between healthy and diseased patients were made.

Interestingly, Colleluori *et al.* compared the effects of an aerobic, resistance and combined training program in obese and frail older adults (together with weight management). There was no difference in vastus lateralis nuclear factor kappa B (NF-κB), TNF-α or interleukin (IL) 6 expression compared to baseline in any of the groups, but TLR2 was significantly upregulated in the aerobic group only, albeit to a minimal degree (1.25-fold).(40)

Chronic exercise program – not otherwise classifiable

Lundeland *et al.* and Shimizu *et al.* organised training camps (a 7-day ranger training course and a 6-day kendo camp respectively) for the (trained) participants with repeated blood sampling. In the trial by Lundeland *et al.*, no significant changes in flow cytometric TLR4 expression were recorded. *Ex vivo* stimulation assay, however, did show increased cytokine production at day 3, followed by normalisation at day 5.(110) Shimizu *et al.* reported higher counts of TLR4-positive monocytes after 3 days, which persisted 7 days after ending of the camp.(167)

Rodriguez-Miguelez *et al.* assessed the impact of a whole body vibration program in seniors and demonstrated decreased protein levels of TLR2 and TLR4 in PBMC, together with lowered levels of signalling pathway molecules (MyD88, TRIF, p65) and concordant cytokine alterations (lowered TNF-α and raised IL-10).(155)

McFarlin *et al.* observed lower TLR4 expression in young and elderly subjects with an active lifestyle in comparison to their inactive counterparts, but no impact of age was recorded. (115) In a different trial, the same group compared baseline TLR4 expression in trained and untrained elderly women (before subjecting them to an exercise bout), and reported lower TLR4 expression in the trained group.(116) In a similar fashion, Flynn *et al.* subjected resistive-trained elderly women to a resistance training program, and used sedentary women who continued their normal activities as comparison. Lower TLR4 expression was reported in the trained group, although it is unclear which proportion can be attributed to the program and which to the preceding active lifestyle.(58) However, contrary results have been published. Timmerman *et al.* found that self-reported physical activity was not significantly correlated with muscle TLR4 protein level.(186) Also Ferrer *et al.* used questionnaires to assess physical activity and demonstrated higher TLR2 and comparable TLR4 levels in the most active elderly compared to the most sedentary, albeit with lower

plasma IL-6 and higher IL-10 gene expression.(62) The latter observations match those of Zheng *et al.* who compared physically active and sedentary students and reported higher mRNA levels of TLR2, TLR7 and MyD88 in the exercise group. TLR4 expression did not differ between both groups.(212)

DISCUSSION

General conclusion regarding the impact of exercise on TLR

Based on the aforementioned findings, a number of propositions can be made. Firstly, resistance exercise bouts seem to have an activating effect on TLR signalling in healthy individuals. This is in line with expectations as resistance exercise is classically considered a trigger of a robust inflammatory response, both local and systemic.(51) Repeated eccentric contractions cause damage to muscle and connective tissue with leakage of intracellular proteins. The exercise-induced muscle damage not only causes the typical delayed onset muscle soreness, but also underlies the ensuing hypertrophic response.(3) The two studies that did not demonstrate alterations in TLRs in response to acute resistance exercise were conducted in elderly women, which makes it tempting to refer to age-related blunting of the immune system. This contrasts with the review of Cavalcante *et al.*, who concluded that acute resistance exercise generally provokes a decrease in TLR expression.(27)

Secondly, an aerobic exercise bout seems to have less activating potential with regard to the TLR-system. In non-healthy subjects, generally unchanged TLR levels were observed. In healthy participants, also downregulatory responses, with even reduction of pathway molecules and cytokine end products, were reported in a significant number of articles. However, especially after intense bouts of longer duration, also upregulatory responses were recorded. These findings are in agreement with a recent systematic review on exercise and inflammation (without looking into the role of TLRs), which concluded that intensity and duration determine the magnitude of the inflammatory response that ensues a bout of exercise. Varying degrees of tissue damage could be a plausible explanation for the impact of these exercise characteristics. However, the same systematic review reported that the increase in inflammatory markers was not accompanied by a parallel increase in creatine kinase (CK) activity, which is considered a marker of muscle damage.(28)

Lastly, it seems that chronic exercise programs involving resistance training predominantly result in unaltered or decreased expression levels of TLRs and associated pathways and cytokines. In aerobic training programs, relatively more increased expression levels were recorded, although the majority of assessments still showed stable levels.

Cross-sectional analyses produced more ambiguous data regarding the effects of chronic physical activity. However, inherent to the trial design, these studies face difficulties with reliable quantification of physical activity and are highly susceptible to confounding factors in relation to an active lifestyle.(209)

Factors such as population studied (including baseline training status), exercise characteristics, the heterogeneous nature of exercise itself, environmental conditions (which could be related to induction of HSP synthesis), time of measurement and analytical method are likely responsible for the disparities in the reported results.(51, 67)

Animal studies may provide additional insight. In the systematic review of Rada *et al.*, it was reported that exercise training globally resulted in TLR downregulation, whereas acute interventions tended not to affect TLR expression.(145) In the present literature study, we observed equivocal responses following aerobic exercise training, with no predominant downregulatory trend present. The response after an acute exercise bout was more in line with the previously mentioned systematic review, as mainly unaltered and downregulatory responses were recorded.

Are alterations in TLR expression a bystander phenomenon of cell shifts?

Most investigators have focused on TLR expression on circulating leukocytes, and more specifically on monocytes. However, it seems often forgotten that exercise has a profound impact on the composition of the monocyte subsets present in the peripheral blood. Booth *et al.* already criticised the fact that the majority of studies do not take the altered monocyte composition into account when reporting on TLR expression.(17) Of note, the blind-sided focus on CD14-expressing cells does neglect the fact that TLRs are also expressed on other cells, for instance neutrophils, circulating progenitor cells, B-, T-, natural killer and dendritic cells.(130) These cell populations are also subject to exercise-induced cell shifts.(121) The relative importance of differences in TLR expression across different immune cells is currently not known.(153) However, it is certain that TLRs also fulfil important functions in these cell types, for instance in neutrophils were TLRs are implicated in cytokine production and cell survival.(43, 153) In the following paragraphs, we discuss the exercise-mediated alterations in leukocyte populations in the studies considered in this review.

Acute exercise

It is well known that acute exercise induces leukocytosis.(43) Factors as blood shear forces, body temperature, catecholamines, corticosteroids and cytokines are held responsible for the recruitment of cells into the blood stream.(23, 43, 48) This is considered an evolutionary conserved response to physical stress, preparing the body for potential injury or infection.(128) Typically, 'recovery' to the baseline leukocyte counts is observed within 24 hours.(117) Although the leukocyte shifts strongly varied between studies, a general trend of increased counts with normalisation within 24 hours could be discerned.

Figure 3 summarises the results of the 4 studies that evaluated shifts in monocyte subsets in response to an acute exercise bout. Exercise seems to increase the proportion of $CD14^{++}$/$CD16^{+}$, and especially $CD14^{+}$/$CD16^{++}$ cells. However, already after 1 hour of recovery, a reverse shift occurs. A fifth study showed similar results, but exact values were not available for inclusion.(146) The preferential mobilisation of pro-inflammatory monocytes to the circulation complicates the evaluation of exercise-induced alterations in TLR expression. However, this also means that reports on stable or lowered TLR levels are not merely the result of shifts in subpopulations, and this actually strengthens the relevance of these findings. In addition, some of the expression changes clearly exceed the magnitude of the parallel shifts in cell composition.(2)

Four groups evaluated the effects of exercise on TLR2 and TLR4 expression on individual monocyte subsets. The results are summarised in Figure 4. The majority of studies showed no changes of expression per subset.(17, 43, 170, 173) However, the few TLR expression changes that did occur, strengthen the assumption that there are more profound effects of exercise on TLR than just cell shifts.(2)

Two studies looked into dendritic cell shifts after exercise bouts (in both cases a marathon run). Running times were comparable and both studies expressed dendritic cells as a proportion of the total leukocyte count. The results were similar with conventional dendritic cell (cDC) proportion increasing and plasmacytoid dendritic cell (pDC) proportion decreasing immediately after the run. Re-measurement after 24 hours showed a tendency towards normalisation.(92, 129)

Chronic exercise

With regard to studies that investigated the effects of chronic exercise programs, generally no differences in total leukocyte count or leukocyte subpopulations (granulocytes, lymphocytes and monocytes) were described.(10, 11, 35, 41, 52, 58, 115, 128, 130, 142, 153, 167, 180) Only three studies reported (relatively minor) alterations for which we refer to Supplementary Tables 5-7.(22, 54, 168)

Five studies looked into the impact of chronic exercise on the distribution of monocyte subsets. Bartlett *et al.* performed two endurance regimen studies with assessment of monocyte distribution. In both cases, no alterations in total monocyte counts were observed. However, endurance exercise training increased the proportion of $CD14^{+}/CD16^{-}$ monocytes and reduced $CD14^{++}/CD16^{+}$ and $CD14^{+}/CD16^{++}$ cells.(10, 11) Similarly, Markofski *et al.* and Timmerman *et al.* reported reduction of the proportion of $CD14^{+}/CD16^{+}$ cells after a resistance training program and combined training program, respectively.(112, 187) On the contrary, Child *et al.* failed to find differences in monocyte subpopulations after their 2-week high-intensity training program.(35)

One study assessed TLR expression on monocyte subsets and reported no change of TLR2 or TLR4 expression on $CD14^{+}/CD16^{-}$ monocytes, but decreased TLR2 expression on $CD14^{++}/CD16^{+}$ and (limited) decrease in TLR4 expression on $CD14^{+}/CD16^{++}$ monocytes after the training program.(10) Only one group studied the impact of a resistance training program and demonstrated that the increased baseline proportion of $CD14^{+}/CD16^{+}$ monocytes in physically inactive, overweight individuals were reduced (to levels observed in active individuals) after the program.(112)

Regarding combined regimens, also Timmerman *et al.* reported higher baseline $CD14^{+}/CD16^{+}$ counts and proportions among physically inactive subjects, with normalisation after completion of their program.(187)

Reductions of inflammatory monocytes are most likely not indicative of increased infiltration into the tissues or migration towards lymphoid organs as murine studies have reported reduced leukocyte infiltration after exercise training.(87, 90, 174)

The impact of chronic exercise on DC subsets was evaluated by Lackermair *et al.* who noted stable cDC counts but lower pDC counts after 4-week preparation on a marathon run.(92) Nickel *et al.* saw similar trends in their obese subgroup, with higher baseline pDCs and lower cDCs compared to the lean groups and increase in cDC and decrease in pDC after the endurance exercise program.(130)

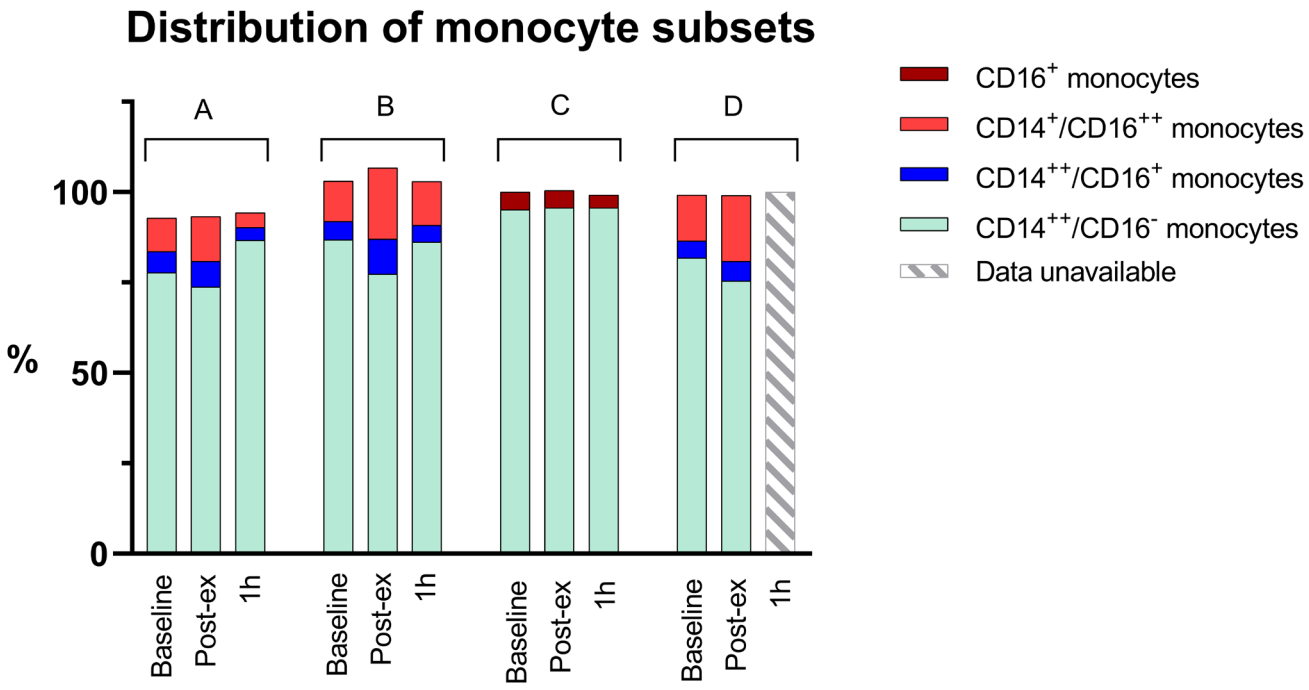
Mechanistic insights into the modulating effects of exercise on TLRs from the included human studies

As mentioned in the introduction, numerous factors have been proposed to explain the relationship between exercise and TLRs. Nevertheless, sound evidence *pro* or *contra* is lacking for the majority of factors. In the next paragraphs, we summarise current hypotheses linking exercise and TLR signalling. For each hypothesis, the most important findings of the articles included in this review are discussed. As this concerns several of the hypotheses, we would like to mention that Booth *et al.* provided evidence against an important role for serum soluble factors in general. They reported increased TLR2 and TLR4 expression on monocytes after exercise, but incubation of resting monocytes with post-exercise serum did not affect TLR expression.(17) However, a trend for elevated TLR4 was observed and the serum kinetics of soluble factors are not always accurately reflected when samples are taken at predefined time points.(110)

Myokines: it is well established that skeletal muscle acts as an endocrine organ with secretion of cytokines and small muscle-derived proteins, collectively termed 'myokines'.(2, 22, 27) In fact, cytokines released in the context of exercise are mainly produced and secreted by skeletal muscle. In contrast, cytokines released during chronic inflammatory diseases are supposed to originate from activated immune cells.(22) According to a recently introduced concept, skeletal muscle-induced anti-inflammatory myokines could even alter the inflammatory status of circulating immune cells.(174) It was suggested that cytokines released into the circulation are capable of exerting feedback on the TLR pathway.(96, 129) As such, a regulatory loop between TLRs and cytokines would exist.(154) For example, *in vitro* work has shown that IL-4 can downregulate monocyte TLR2 and TLR4 expression and that interferons can upregulate several TLR genes.(69, 120, 156, 176) Also IL-6 (which is typically elevated after exercise) and IL-1 (as the IL-1 receptor and Toll-like receptors share a similar cytoplasmic signalling domain) have been mentioned as candidates to explain the exercise-TLR interaction.(58, 136) None of the included articles could provide further information on the role of myokines in the relationship between exercise and TLRs.

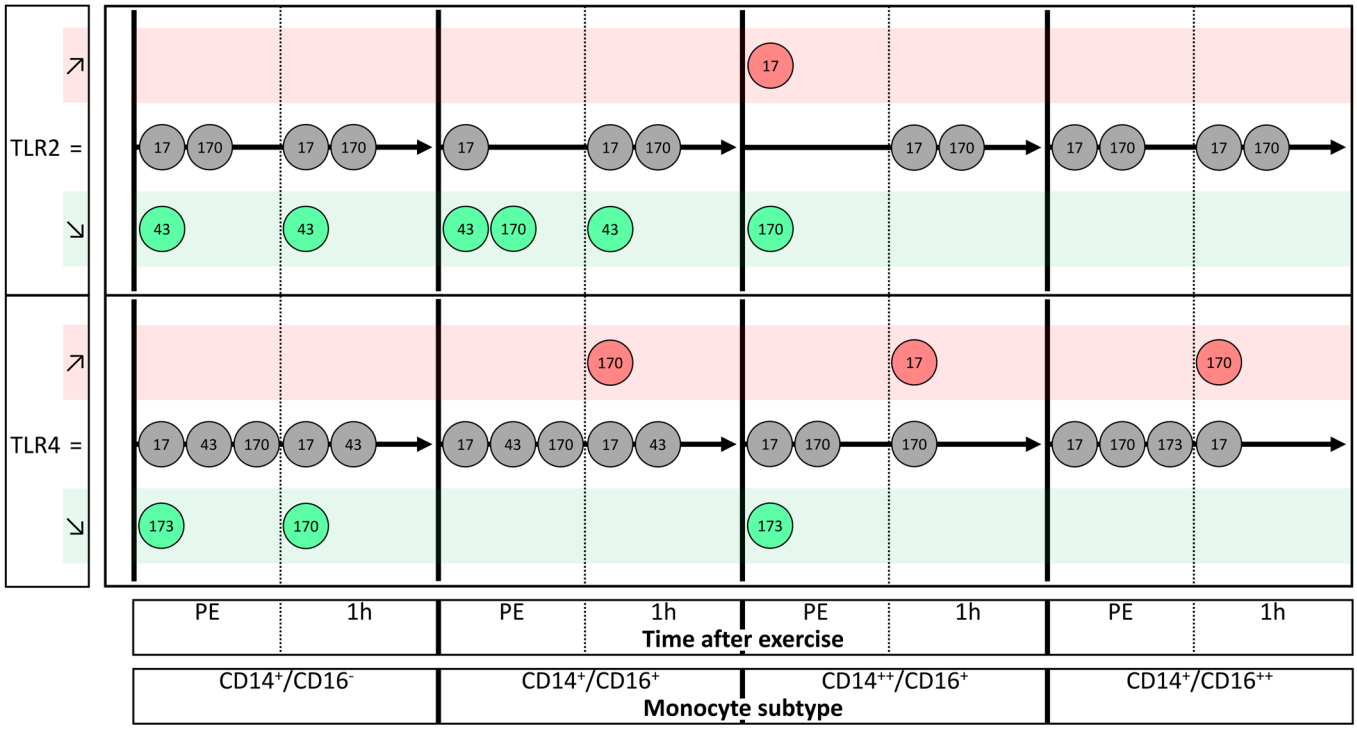
Obesity and hyperglycaemia: obesity and type 2 diabetes mellitus are associated with a pro-inflammatory status, both at cellular, TLR (including signalling pathway) and cytokine level.(10, 12, 38, 43, 108, 112, 115, 116, 129, 130, 142, 150, 174, 175, 187) A central role for adipose tissue has been proposed, related to the secretion of a variety of cytokines ('adipokines'). Increased levels of inflammatory adipokines, and reduced secretion of anti-inflammatory adipokines (*e.g.* adiponectin) would contribute to the observed systemic inflammation.(68, 103, 142) In addition, hyperglycaemia and fatty acids have been linked to TLR activation and increased TLR surface expression.(25, 43, 153, 174, 182) It has been argued that the anti-inflammatory effects of exercise are mediated by a change in body composition.(43, 112) However, numerous studies have

Figure 3 | Acute exercise-induced shifts in monocyte subsets.



The X-axis denotes time post exercise, with "post-ex" signifying immediately after (aerobic) exercise. The Y-axis represents the total monocyte proportion expressed as percentage. Deviations from 100 % are due to mathematical rounding. A) Simpson *et al.* 2009 (170); B) Booth *et al.* 2010 (17); C) Durrer *et al.* 2017.(43) The distinction between $CD14^{++}/CD16^{+}$ (intermediate) and $CD14^{+}/CD16^{++}$ (non-classical) monocytes was not made. Only the data of the healthy controls were considered; D) Slusher *et al.* 2018.(173)

Figure 4 | Impact of acute aerobic exercise on TLR expression on individual monocyte subsets.



The X-axis denotes the monocyte subpopulation and time after exercise, with post-exercise (PE) signifying immediately after exercise. The Y-axis indicates the change over time: increase (arrow up, red zone), stable levels (centre, white zone) or decrease (arrow down, green zone). Note that the $CD14^{+}/CD16^{+}$ category comprises both $CD14^{++}/CD16^{+}$ and $CD14^{+}/CD16^{++}$ cells. Each circle represents one study. The numbers in each circle are the corresponding reference.

demonstrated that the salutary actions of exercise are not (or at least not entirely) dependent on its effect on adipose tissue.(95, 174) Stewart *et al.* and Timmerman *et al.* have demonstrated that their combined training programs did not affect body fat percentage, but did significantly reduce the number of inflammatory monocytes.(180, 187) Child *et al.* reported that 2 weeks of high-intensity interval training (HIIT) did not change BMI or waist-to-hip ratio, but monocyte TLR4 expression was increased.(35) Markofski *et al.* subjected physically inactive adults to a resistance exercise program with one of the groups also receiving an energy restriction diet. The BMI and body fat percentage did not change in the resistance training only group, in contrast to the group that also received the diet intervention. Remarkably, only the group without diet intervention demonstrated decreased pro-inflammatory monocytes and LPS-stimulated TNF-α and IL-6 production.(112) Lambert and colleagues reported similar findings. In their study, muscle tissue TLR4 expression was reduced in the group that underwent a combined training program, but not in the group that received an energy-deficit diet (although both groups had reduction of the fat mass).(94)

The study of Robinson *et al.* provided information on the role of hyperglycaemia in the exercise-TLR interaction. Obese, sedentary prediabetic patients were subjected to short-term training, aimed to minimise alterations in body composition. Their moderate-intensity continuous training (MICT) protocol significantly reduced fasting plasma glucose, whereas the high-intensity training protocol failed to do so. The fact that they found reduced TLR4 expression on monocytes and lymphocytes after both training protocols, argues against plasma glucose as important mediator.(153)

Endotoxemia: obesity, type 2 diabetes mellitus and high-fat feeding are associated with increased circulating endotoxin levels, which is referred to as 'metabolic endotoxemia'.(18, 61) Also strenuous exercise can increase translocation of LPS from gut bacteria into the circulation.(17) It was demonstrated that even low-dose circulatory LPS can trigger TLR pathways.(208) On the contrary, it seems that chronic exercise decreases the gut permeability, hereby reducing TLR signalling activation.(39) At present, insufficient data is available to evaluate the significance of endotoxemia in the proposed relationship between exercise and TLRs. Jin *et al.* studied 20 obese middle-aged women and concluded that their combined training program suppressed the peak postprandial endotoxemia, but TLRs were not evaluated.(82)

Fatty acid (FA) composition: another mechanism relates to the effect of exercise on fatty acid composition of blood and tissue lipids. In their extensive review, Nikolaidis and Mougios concluded that exercise leads to an acute increase in unsaturated (especially monounsaturated), non-esterified fatty acids (NEFAs) in the plasma.(132) This is not surprising as NEFAs are an important metabolic fuel. Noteworthy, NEFAs are able to activate TLR2 and TLR4, although direct binding remains uncertain.(198, 211) Zhou *et al.* reported that *in vitro* free fatty acid treatment of bone marrow-derived macrophages of diet-induced obese (DIO) mice downregulated TLR2 expression, which could fit the proposed mechanism of downregulation by exposure.(214) Chronic exercise seems to increase the proportion of polyunsaturated FA (PUFA) and omega-6 FA and decrease the relative amount of monounsaturated FA in adipose tissue.(132) PUFAs can inhibit agonist-induced TLR4 activation.(110) Of the included trials, only four determined plasma NEFA level.(11, 12, 24, 65) In none of the studies, significant differences in baseline or post-exercise values between young and old or between obese, diabetic or athlete participants were recorded. Two trials evaluated the response to acute exercise, both of which observed higher levels in conjunction with an aerobic bout, as would be expected.(12, 24) One of the aforementioned trials also determined NEFA level during recovery (2 hour post-exercise), and recorded even higher values. In contrast, muscle TLR4 protein (and other molecules involved in TLR signalling) levels remained unaltered during and after the exercise bout.(12) Two groups that evaluated the effects of an endurance exercise program did not detect significant changes in NEFA level after completion.(11, 65) Currently, there is no evidence to support the hypothesis that exercise causes cascade activation of TLRs through increased levels of NEFAs.(95, 198) Moreover, it was very recently demonstrated that long-chain saturated fatty acids are not TLR4 agonists after all.(97)

Corticosteroids: physical activity elicits endocrine responses, including elevated levels of corticosteroids (gluco- and mineralocorticoids).(31, 109) It was shown that this upregulation involves IL-6 mediated stimulation of the adrenal glands.(27) Corticosteroids have far-reaching effects on the immune system, including selective depletion of inflammatory monocytes and modulation of NF-κB transcriptional activity.(96, 187) In human corneal fibroblasts, hydrocortisone-mediated reduction of mRNA and protein expression of TLR2 and TLR4 has been demonstrated.(83) As such, they have been considered as candidates to explain the effects of exercise on the TLR system.(96) However, there are several arguments that argue against an important role for glucocorticoids in the regulation of TLR expression *in vivo*. Lancaster *et al.* could not demonstrate circadian rhythmicity in TLR1, 2, 4 or 9 expression on $CD14^+$ monocytes, despite plasma cortisol concentration being more than two times higher in the morning compared to the evening. In addition, the plasma cortisol concentration immediately after exercise was not different from the pre-exercise value, which contrasts with already significant alterations in TLR expression immediately after exercise. In the same study, it was also demonstrated that LPS and zymosan stimulation differentially affected intracellular IL-6 expression in monocytes taken from post-exercise blood samples. This finding contrasts with the suppressive effect of dexamethasone in physiological concentrations on LPS- and zymosan-stimulated intracellular monocyte IL-6 production.(96) *Ex vivo* research from other investigators using dexamethasone incubation produced inconsistent results regarding TLR expression, with differences between receptors and within a single receptor.(69) The training program of Bartlett *et al.* reduced the expression of TLR2 and TLR4 on monocytes, but plasma cortisol was unchanged.(10) These arguments of course do not exclude the possibility that corticosteroids exert their effects indirectly, *e.g.* via cytokines or alterations in leukocyte subpopulations.(69)

Heat shock proteins: HSPs are a family of intracellular proteins that function as molecular chaperones by supporting the folding, unfolding and transport of other proteins.(58, 66, 180)

They are upregulated in stress conditions to protect the cell.(58) However, HSPs can also act as cytokines ('chaperokines') when released from damaged tissue, *e.g.* by activating TLR2 and TLR4.(58, 66, 180) HSP60 and HSP70, two highly conserved and expressed members, are among the many DAMPs recognised by TLR2 and TLR4.(76, 154) Nevertheless, increased HSP levels might actually be beneficial. Repeated exposure to HSP60 induces a tolerance to HSP and cross-tolerance to LPS stimulation, presumably through downregulation of TLR4.(76, 94, 136, 180) In addition, HSP70 seems to block NF-κB activation at different levels.(76, 136) So perhaps HSP shouldn't be considered as DAMPS, but rather as DAMPERs. It remains to be investigated whether HSPs can also transmit anti-inflammatory signals through (instead of by blocking) the TLR signalling cascade.(193) Exercise transiently increases HSPs in an intensity- and frequency dependent manner.(124, 128, 141, 154, 156) Both glucocorticoids and catecholamines could be involved in this HSP response.(139) The available evidence suggests that HSPs are potential candidates to explain the effects of exercise on TLRs, but further research is warranted.(180) In the study of Falgiano *et al.* TLR4 and HSP70 expression showed similar kinetics, with both protein levels being downregulated one hour after exercise compared to 4 hours after.(48) Also chronic exercise can modulate HSP levels. An 8-week training program in healthy seniors led to increased protein levels of HSP70 and decreased levels of HSP60. TLR2 and TLR4 protein content was decreased after the end of the program.(154) Young female handball players showed no increase in extracellular HSP70 throughout their training season, but the lymphocyte HSP70 content was higher at the middle and end of the season compared to the beginning.(199) There are, however, also (low-intensity) training programs that failed to see changes in HSP expression.(169) Exertional heat stress is thought to have a direct effect on TLRs, independent from HSPs.(194) However, Gleeson *et al.* observed surface downregulation of TLR1-TLR4 after a cycling bout without alterations in body core temperature.(69) The same group also incubated $CD14^+$ monocytes at different temperatures (22°C, 37°C and 40°C) and found no effect on CD14, TLR1, TLR2 or TLR4 expression.(69) This is in line with the results of Zhou *et al.* who demonstrated that prolonged incubation at 42°C did not change cell surface expression of CD14, TLR2 or TLR4 on human monocytes (despite upregulation of TLR2 and TLR4 mRNA and cytoplasmic HSP70 content).(213) Capó *et al.* reported that their maximal exercise test increased core (up to 39°C) and skin (up to 34.8°C) temperature in young and old athletes, but no differences in TLR gene expression in PBMC were observed.(24) On the other hand, VanHaitsma *et al.* demonstrated that acute exercise in temperate or hot conditions both reduced TLR4 expression, but the suppression persisted substantially longer in the group that exercised in hot conditions.(194)

Nucleic acids: cell-free DNA (cfDNA) and microRNA: it has been well established that circulating cfDNA concentrations increase immediately after exercise, with a rapid return to baseline. Circulating DNA is one of the known DAMPs for TLRs.(19) Growing evidence suggests that miRNAs can modulate immune functions in response to exercise.(39) MiRNAs readily appear in plasma and leukocytes following an exercise bout. Further, chronic exercise training can modulate circulating miRNA responses.(2, 8, 39) For the role of cfDNA in the exercise-TLR interaction, data are currently lacking, but for miRNAs, scarce evidence is available. Radom-Aizik *et al.* evaluated the effects of 30 min of strenuous exercise on miRNA expression in young healthy men in two different trials.(146, 147) In the first trial, exercise altered expression of 34 miRNAs in PBMCs, of which many were involved in inflammatory processes.(147) In the second trial, the expression of 19 miRNAs was altered in monocytes, again including miRNAs related to inflammation.(146) Among others, exercise alters expression of miRNA-132, miRNA-125b and let-7e, which are known to regulate TLRs in monocytes.(147) In addition, TLRs have also been proposed as receptors for circulating miRNAs, although the significance of this finding remains unclear.(47)

Reactive oxygen species (ROS): it is well known that oxidative stress levels are modulated by physical activity. Regular exercise downregulates oxidative stress.(46) On the contrary, unaccustomed and/or exhaustive exercise can generate excessive ROS.(27, 75) ROS have the potential to activate NF-κB and mitogen-activated protein kinase (MAPK) pathways and to modulate the intracellular TLR signalling cascades which converge to these same pathways.(65, 161, 181, 204) In addition, it has been reported that ROS production can upregulate TLR expression.(167, 181)

Three studies looked into oxidative stress levels. Cheng *et al.* reported downregulation of TLR4 mRNA, upregulation of superoxide dismutase and catalase, and reduced levels of hydrogen peroxide (H_2O_2) after their lower back training program. They suggested that upregulation of the inflammation related gene sirtuin-1 may be the link between exercise and the beneficial effects on oxidative stress.(34) On the other hand, Falgiano and colleagues reported downregulation of TLR4 and sirtuin-1 immediately after exercise, with similar kinetics.(48) Ferrer *et al.* categorised elderly volunteers according to self-reported physical activity and found higher TLR2 levels in active participants compared to their sedentary counterparts, but without differences in myeloperoxidase (MPO) levels.(54) The aerobic training program of Estébanez *et al.* did not change TLR4 protein levels, or oxidative stress biomarkers.(46)

Matrix metalloproteinases (MMPs)-mediated TLR shedding: MMPs are a class of enzymes that participate in ectodomain shedding.(39) The limited data available suggests that exercise modulates MMP levels.(127, 160) MMP-mediated ectodomain shedding could contribute to decreased TLR expression on immune cells after exercise.(39, 43) Additionally, the TLR ectodomain can negatively regulate TLR activation by acting as a decoy receptor.(98) However, at present, no evidence is available linking exercise to MMPs and soluble and membrane-bound TLR levels. The hypothesis of exercise-induced TLR shedding remains to be tested.

Mechanistic insights into the modulating effects of exercise on TLRs from animal studies

The majority of animal research on TLRs has been conducted in rodents. In general, comparisons of animal and human TLRs is complicated by substantial interspecies differences (includ-

ing transcriptional regulation and cellular expression).(69, 77, 149) To the best of our knowledge, no animal research with the specific purpose to elucidate the link between exercise and TLRs has been performed. However, regarding the aforementioned hypotheses, several observations are worth mentioning.

Firstly, some studies have reported that changes in TLR expression in response to exercise may be tissue specific, while others failed to find such differences.(104, 105, 107, 159) Regarding the mechanism(s) underlying the exercise-TLR interaction, a regulatory feedback loop through myokines remains a viable hypothesis. Several studies have simultaneously compared myokine and TLR expression, thereby supporting this association, but no conclusive information on causality was provided.(37, 81, 86, 105, 107, 114, 135, 156, 183, 210) Ropelle *et al.* reported that injection of recombinant IL-6 did not change TLR4 expression in rats with diet-induced obesity, although only hypothalamic tissue was evaluated.(158)

Animal research has provided additional arguments against the hypothesis that changes in body composition mediate the effects of exercise. Carpenter *et al.* demonstrated that sedentary DIO mice with weight loss showed increased monocyte TLR expression, in contrast to voluntary running DIO mice with weight loss who showed decreased TLR expression.(25) Similarly, two studies demonstrated that (forced) exercise training did not induce loss of body weight or adipose tissue in high-fat diet-fed mice, while exercise did reduce the higher TLR4 levels in these mice.(45, 87) Interestingly, it has been shown that TLR4 itself influences murine body composition. TLR4-deficient mice fed a high-fat diet gained less body fat compared to wild-type mice.(84)

Further, studies in rodents have generated evidence against a driving role of endotoxin and corticosterone. In the rat study by Liao *et al.*, downhill running resulted only in a very late (24 hours after exercise) increase in muscle endotoxin levels. In contrast, TLR4 mRNA changes were already observed 1 hour after exercise.(105) Lira *et al.* confirmed in a murine model that overtraining increases circulating endotoxin levels. Also corticosterone levels were elevated in the overtrained group. Nevertheless, hepatic and adipose tissue TLR4 protein content was not altered.(107) Oliveira *et al.* demonstrated in rats that exercise reduced TLR4 mRNA levels in adipose tissue, but no impact on serum corticosterone was observed.(135)

As in humans, HSP70 concentrations in animals increase in an intensity- and frequency-dependent way after exercise.(39, 154, 211) No further information on the validity of the hypothesis that HSPs plays an important role in the effect of exercise on TLRs is available from animal research.

In addition to the aforementioned miRNAs, Wu *et al.* reported that aerobic exercise increases miRNA-126 and miRNA-146a, while reducing TLR4 protein expression.(203) Interestingly, it has been shown that miRNA-146a can negatively regulate TLR4.(206) Further research has revealed that miRNA-146a can interact with the TRAF6 gene (which is involved in the non-MyD88-dependent TLR signalling pathway), negatively modulating its expression.(203)

Animal research has provided mixed results regarding the role of ROS. In the trial by Li *et al.* in rats, malondialdehyde (MDA) and superoxide anions showed a similar response to exercise compared to TLR2 and TLR4 mRNA and protein levels.(104) Similarly, in the trial by Rodriguez-Miguelez, MPO showed a parallel pattern after exercise as the TLR4 level.(156) On the contrary, Liao *et al.* observed a delayed increase in MPO and hydrogen peroxide, whereas TLR4 mRNA rapidly decreased after exercise, and remained decreased.(105)

Lastly, *in vitro* work by Chen *et al.* using C2C12 myoblasts has shown that mechanical stretch inhibited TLR3 expression. The precise molecular mechanism by which mechanical strain regulates TLR3 levels is not yet clear, but this could be very relevant in the context of exercise and TLRs.(32)

In summary, the limited data available in animals and humans make it difficult to draw definite conclusions regarding the underlying mechanisms of the observed TLR changes. However, as discussed above, it currently seems unlikely that these are mediated by changes in body composition, serum glucose, serum fatty acids or serum corticosteroids. Further research is required to determine the factors underlying the relationship between exercise and TLRs. Several mechanisms are likely to be involved simultaneously.

Heterogeneity in the methodological approach

Critical remarks need to be made regarding some of the diagnostic methods and reported results.

Only 7 studies simultaneously applied different analytical techniques to assess the same TLR molecules.(51, 52, 54, 108, 116, 129, 130) Although the majority of results were concordant or trending towards concordance, completely opposite results at transcript and protein level were also reported. This was also the case for molecules involved in the TLR signalling cascade and cytokines in other studies.(52, 156) In general, correlations between mRNA and protein expression levels are notoriously poor, although this is also dependent on the gene class. It is known that genes that are differentially expressed by experimental manipulation are more likely to show concordant protein expression across the same experimental conditions.(91) Interestingly, Guo *et al.* performed a mRNA-protein correlation study in human circulating monocytes. They concluded that genes belonging to the extracellular region of cell components and genes with signal transducer activity showed the highest correlation, however, expression at mRNA level was found to be generally informative but not predictive for that at protein level.(71) From this perspective, it is problematic that 25 studies solely determined TLR expression at transcript level, as proteins should still be regarded as the major direct executors. Perhaps, TLR internalisation and/or shedding are in part responsible for the observed discrepancies.

Most researchers studied repetitive venous blood samples. However, as plasma cytokines originate from 'spill over' from various organs and tissues, important changes at the cellular level may not be detected in the plasma.(153) For example, Lambert *et al.* showed decreased expression of IL-6 and TNF-α in muscle tissue in response to a combined training program, but not in the serum.(94) Therefore, peripheral blood findings cannot be generalised to tissue responses.(48) Immune responses may also vary in different parts in the body.(110) Nevertheless, assessment of blood monocytes may be a good proxy/convenience measure of TLR expression and inflammatory capacity of macrophages found in different tissues (*e.g.* adipose tissue and skeletal muscle). These peripheral tissue macrophages are deemed to be to a large extent responsible for whole body chronic inflammation.(69, 95)

Whole blood stimulation assays (frequently using LPS

as TLR-stimulant) is a commonly used technique to correlate findings on expression level with functional alterations. However, when making such correlations, it should be considered that also other cells besides monocytes can respond to LPS stimulation.(112, 173) Some of the effects of exercise only became evident after stimulation assay (and were not visible in native plasma or unstimulated cultures), which raises the question whether these results are reflective of (the complex) *in vivo* responses.(1, 2, 68, 96, 110, 121) In addition, large heterogeneity was found regarding incubation times, cell preparation and stimulant dose.(172)

The unit of expression is of critical importance for reporting of the results. For example, in the study of Niemiro *et al.*, the proportion (%) of progenitor cells expressing TLR4 was unchanged, but the concentration (cells/μL) of progenitor cells with surface TLR4 decreased, and the TLR4 expression level (median fluorescence intensity) increased.(131) Capó *et al.* used a PBMC stimulation assay. Acute exercise increased cytokine production in response to LPS. However, no differences were observed when results were expressed per monocyte, but these results were not shown.(23) Also Durrer *et al.* reported different results between absolute and leukocyte-corrected cytokine release following a stimulation assay.(43) Another study noted that the number of monocytes that responded to LPS stimulation by producing interleukines was increased, but that the stimulated cells produced less interleukines.(178) This is in contrast to the observations of Markofski *et al.* who saw no differences in stimulated cytokine production when corrected for the number of monocytes, but did find lower numbers of inflammatory monocytes after exercise.(112)

We would like to make a concluding remark regarding physiological variation that can potentially influence the results. The research group of Lancaster investigated diurnal rhythmicity of TLR expression and activation. Monocyte surface expression of TLR1, 2, 4 and 9 showed no difference between morning and evening samples. Neutrophil expression of TLR1, 2 and 4 also remained constant, but TLR9 was expressed at lower levels in the evening. Upon *ex vivo* stimulation, monocyte expression of costimulatory molecules was significantly greater in the evening samples.(96)

It was also demonstrated that monocytes of normal healthy subjects show a decline in LPS-stimulated TNF-α production from summer to autumn.(125)

In summary, we believe that the ideal methodological design should not solely focus on Toll-like receptors, but also take into account downstream pathway molecules and end products. Changes at the transcript level should be correlated to the protein level and *vice versa*. Localisation and trafficking of TLRs could provide insight into the fate of membrane-bound TLRs after exercise. It would also be interesting to compare changes in peripheral blood with those in skeletal muscle. Additional stimulation assays can provide valuable functional information. When reporting the results, researchers should present absolute numbers rather than relative measures.

Functional relevance of the observed alterations

Monocyte surface expression of TLR seems to have clinical relevance as this is known to differ and/or predict outcomes in the setting of sepsis, tuberculosis and chronic liver failure.(17) Furthermore, monocytes from donors who are homozygous for certain TLR4 mutant alleles are clearly hyporesponsive for LPS.(163) In addition, a significant number of studies have found an association between cytokine production in stimulation assays and TLR expression.(22, 43, 96, 115) However, regarding the stimulation assays, also the opposite holds true.(43, 112, 121, 153, 172, 173, 180, 187) Assessment of molecules involved in TLR signalling has varied from consistent regulation of each of the steps to completely conflicting results. This is also the case for plasma or serum cytokines. Cavaillon has dedicated an entire review to the debunking of the simplistic dichotomy of pro- and anti-inflammatory cytokines. Actually, a given cytokine may behave as a pro- and anti-inflammatory cytokine.(26) For example, elevated IL-6 is considered a marker of a pro-inflammatory disease pathology, but systemic injection of IL-6 increases plasma IL-10 concentrations and inhibits TNF-α release after LPS injection in healthy humans.(173, 177)

Furthermore, TLRs are just one of the many factors that determine the immune system functionality. For example, Bartlett *et al.* demonstrated enhanced neutrophil and monocyte phagocytic capacity and oxidative burst, despite decreased and unchanged expression of CD16, TLR2 and TLR4 on monocytes and neutrophils respectively.(10)

It should be noted that also other mechanisms can confer the effects of exercise on TLRs besides gene or protein expression. For example, stimulation by certain ligands could eventually lead to tolerance with reduced TLR responsiveness.(39, 95, 142) In addition, it was recently demonstrated in blood cultures that exercise can upregulate expression of genes involved in the negative regulation of TLR signalling. (2, 43) Overall, it remains however highly conceivable that the exercise-induced alterations in TLRs do have functional consequences.

Transient TLR activation following exercise may actually reflect a positive response that is necessary to facilitate debris clearance from muscle damage and regulate vascular function. (172, 173) Acute bouts of exercise are also held capable of selective clearance of dysfunctional immune cells, improving the functionality of the remaining pool.(10) From an evolutionary perspective, a robust response to a potential threat could actually be beneficial, as long as the response does not persist beyond clearance of the danger.(172) Short-term acute inflammation even allows the body to survive progressive tissue destruction by promoting healing.(27) The impact of acute exercise on TLRs can also be linked to the controversial and highly debated theory that exercise (especially if strenuous or prolonged) leads to a temporary decrease in immune competence.(129) This is referred to as an 'open window' of increased susceptibility for infection.(92, 117, 156) As such, downregulation of TLRs after exercise could be involved. However, to date, there is no hard evidence to support the presumptions that exercise impairs immune cell function or temporarily increases vulnerability for infection.(20) Whether the open window truly exists, is still the subject of intense debate.(2, 48, 129)

On the other hand, the association between sedentarism, aberrant TLR activation, chronic inflammation and numerous chronic disease states underscores that long-term TLR upregulation and/or activation is likely detrimental.(69) As such, the long-term health benefits of exercise could be mediated (in part) by modulation of TLR responses.

Limitations

Despite the value of translational research in experimental animal models, this systematic review was limited to studies reporting TLR in human subjects. Substantial between-study heterogeneity was observed with regard to the investigated population, the exercise intervention, the TLR evaluation method and the reporting of the outcomes, even when the studies were categorised according to exercise modality and study population. Because of the heterogeneity, it was not practicable to perform a meta-analysis on the published results. Lastly, several studies had small sample size, possibly leaving them underpowered to detect an impact of exercise.

Conclusion and future perspectives

To the best of our knowledge, this is the first systematic review that addresses the effects of acute and chronic exercise on TLRs in humans, without exclusions based on TLR type or health status. According to our findings, the effect of exercise on TLRs is dependent on exercise modality and duration. Acute resistance exercise seems to elicit TLR signalling activation. Acute aerobic exercise does not affect, or especially in healthy participants, even lowers TLR levels. Particularly in intense bouts of longer duration, also increased TLR activation was reported. Exercise training programs generally result in stable or decreased expression levels of TLRs. Within these exercise programs, upregulatory responses were almost exclusively described in aerobic programs. However, the substantial heterogeneity between studies limits the generalisability of these findings. Complementary research, paying attention to careful study design, meticulous phenotyping of the study population, shifts in leukocyte populations, analytical methods (correlating findings at transcript and protein level) and analytical target selection (corroborating TLR findings by evaluation of pathway molecules and functional assays) are required. Future studies comparing the influence of different exercise modalities, durations and intensities could add invaluable information to the field. In addition, the impact of the patient characteristics (age, baseline physical activity, health status) on the TLR response to exercise merits further investigation.

Several features suggest that the anti-inflammatory effects of exercise may be mediated through TLR pathway modulation. However, these effects are most likely not limited to TLR alterations. For instance, in this review, we also described reduced presence of inflammatory cell populations after exercise programs.

Finally, the mechanism(s) underlying the effects of exercise on TLRs remain to be elucidated. Several viable theories have been proposed, but sound evidence is lacking. According to our opinion, several factors are most likely involved simultaneously, with host, exercise and environmental characteristics determining their contribution.

Author contributions

KF and MB were responsible for the article selection process, data extraction and quality and bias assessment. Any disagreements were discussed together with the other authors. KF drafted the manuscript. MB, PD, HF, EVC, JDS, IW, GDM, HH and PJG critically reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there are no conflicts of interest.

SUPPLEMENTARY MATERIAL

Toll-like receptor (TLR) signalling pathways

TLRs interact with their respective ligand as a homo- or heterodimer along with a co-receptor or accessory molecule.(88) For example, CD14 is a well-known co-receptor for both TLR2 and TLR4.(59) All TLRs share a similar cytoplasmic signalling domain, the Toll/IL-1 receptor (TIR) domain, that initiates the downstream signalling cascade by differentially recruiting members of a set of five TIR domain-containing adaptor proteins.(80, 88, 133, 188) These signalling cascades are discussed in more detail in the next paragraphs and are schematically illustrated in Supplementary Figure 1.

Myeloid differentiation primary response gene 88 (MyD88) is considered the 'universal adaptor protein' as it is used by all TLRs, except for TLR3.(9, 130) The MyD88-dependent pathway sequentially involves IL-1R-associated kinases (IRAKs), TNFR-associated factor (TRAF) 6 and TGF-β-activating kinase (TAK) 1.(9, 88) TAK1 in turn activates two different pathways. In the first pathway, TAK1 activates the IκB kinases (IKK) complex, leading to degradation of the inhibitory protein IκB.(52, 88) Under normal conditions, IκB binds to nuclear factor kappa B (NF-κB) and retains it in the cytosol.(48, 51, 111) The transcription factor NF-κB is a master regulator of the inflammatory response.(155) Degradation of IκB enables translocation of NF-κB into the nucleus with subsequent activation of a wide variety of genes, including genes encoding pro-inflammatory cytokines.(54) The second TAK1-mediated pathway results in activation of mitogen-activated protein kinase (MAPK) family members, such as extracellular signal-regulated protein kinase (ERK) 1/2, p38 and c-Jun N-terminal kinase (JNK). This ultimately leads to activation of the pro-inflammatory transcription factor activator protein-1 (AP-1).(52, 88)

Alternatively, TLR3 and 4 are capable of signalling through a non-MyD88-dependent pathway. The cascade starts with the recruitment of TIR-domain-containing adaptor protein-inducing interferon-β (TRIF). TRIF interacts with TRAF6 and TRAF3. In this pathway, TRAF6 uses the kinase receptor-interacting protein (RIP) 1 to activate the TAK1 complex, leading to induction of inflammatory cytokines through NF-κB and MAPKs as explained above. TRAF3 recruits TANK-binding kinase 1 (TBK1) and inducible IκB kinase IKKi (also known as IKKε) for phosphorylation of interferon regulatory transcription factors (IRFs) 3 and 7, enabling their translocation to the nucleus where they facilitate transcriptional activation of genes responsible for encoding type I interferons (IFNs).(50, 64, 73, 88, 133, 154, 207) IFNs are multifunctional cytokines that play an important role in the first line defence against viral infections.(101)

Besides MyD88 and TRIF, three other TIR domain-containing adaptor proteins exist. MyD88-adaptor-like (MAL) (also termed TIRAP) and TRIF-related adaptor molecule (TRAM) act as bridging adaptors for MyD88 and TRIF respectively. The fifth adaptor protein, sterile α- and armadillo-motif-containing protein (SARM), seems to negatively regulate NF-κB and IRF activation, although more research is required in this regard.(88, 133)

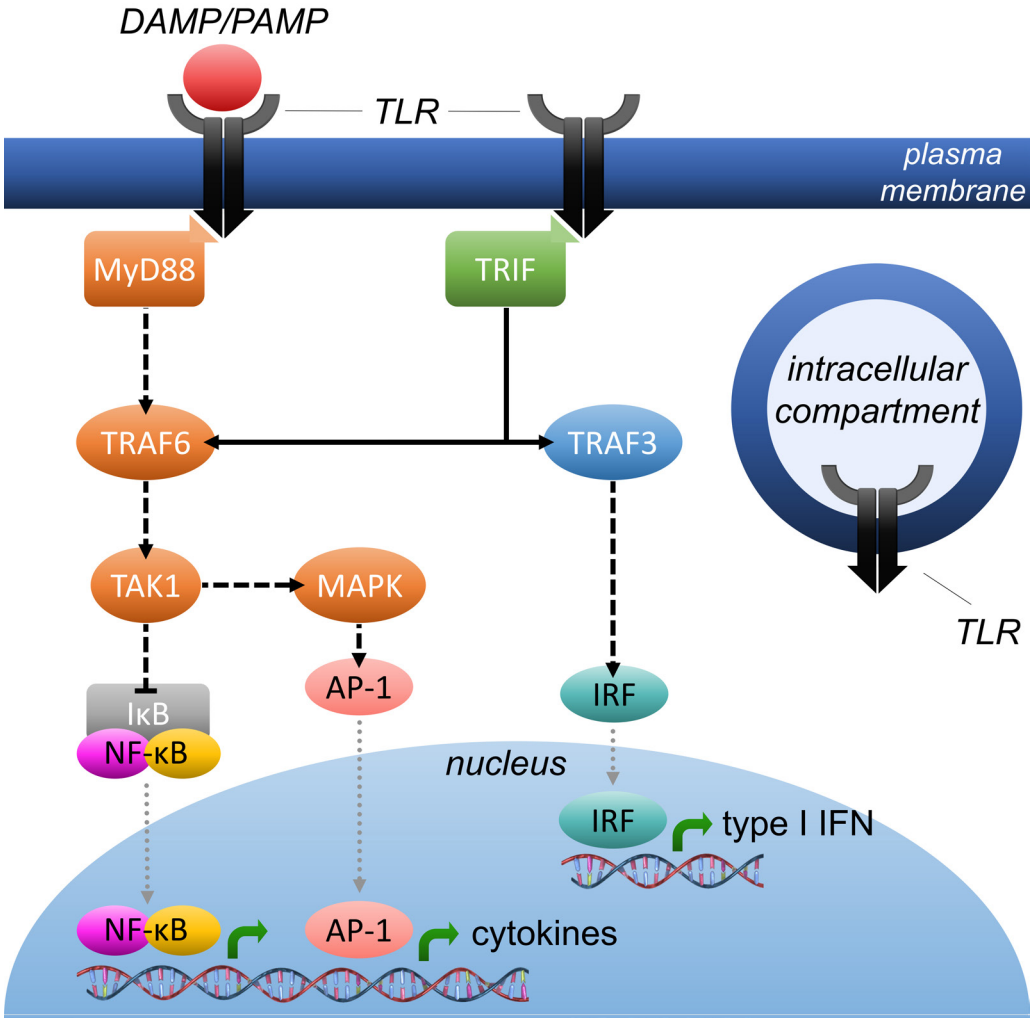
So ultimately, TLR signalling activates transcription factors that promote transcription of a wide variety of genes typically leading to the production of pro-inflammatory cytokines (*i.a.* interleukine (IL) 1, IL-6, tumor necrosis factor alpha (TNF-α), chemokines and type I IFNs).(1, 9, 69) This way, TLRs are pivotal members of the innate immune system. Additionally, TLRs play an important role in priming of adaptive immune responses, including upregulation of antigen-presenting molecules (*e.g.* major histocompatibility complex (MHC) class II), co-stimulatory molecules (*e.g.* CD80/CD86) and specific cytokines (*e.g.* IL-6 and IL-12) in antigen-presenting cells.(9, 69, 96, 136)

Toll-like receptor expression and monocyte and dendritic cell subtypes

TLRs are predominantly expressed in and on immune cells. In exercise literature, most investigators have focused on monocytes and, to a lesser degree, on dendritic cells due to their diverse role in inflammation and immune function.(10, 43)

In monocytes, TLR expression varies according to the subtype. Monocytes are categorised according to the expression of CD-molecules on their cell surface. Classical monocytes express high levels of CD14, but lack expression of the Fc receptor CD16 ($CD14^{++}/CD16^{-}$).(173) Approximately 10-20% of monocytes co-express CD16 and are considered pro-inflammatory. These are further subdivided into an intermediate ($CD14^{++}/CD16^{+}$) subset and a non-classical ($CD14^{+}/CD16^{++}$) subset.(35, 170, 173) Interestingly, pro-inflammatory (CD16-positive) monocytes are characterised by higher surface expression of TLR2 and TLR4.(38, 96, 112, 170, 173, 187) Upon stimulation with lipopolysaccharide (LPS), classical monocytes produce IL-6 (a predominantly pro-inflammatory cytokine) and IL-10 (an anti-inflammatory cytokine). On the other hand, pro-inflammatory monocytes produce IL-6 and the pro-inflammatory TNF-α, but little or no IL-10 following LPS-stimulation.(96, 170, 173) They also express a greater level of HLA-DR (MHC class II) suggesting higher capacity for antigen presentation.(170) It is therefore not surprising that increased circulating levels of pro-inflammatory monocytes are associated with a number of chronic diseases.(38, 112, 187) Dendritic cells (DCs) constitute two major subsets in humans.(42) Myeloid (or conventional) DCs (cDCs) are the largest fraction and use TLRs 1, 2, 4-6 and 8 to detect mainly bacterial pathogen-associated molecular patterns (PAMPs). Upon activation, cDCs secrete pro-inflammatory cytokines and present antigens. Plasmacytoid DCs (pDCs) use TLRs 7 and 9 to detect mainly viral RNA and DNA, respectively.(92) They are less proficient in antigen presentation and react to activation with the production of type I IFNs and other cytokines.(41, 129)

Supplementary Figure 1 | Simplified overview of the MyD88-dependent and –independent signalling pathway in Toll-like receptor activation.



TLR1, TLR2, TLR4-6 and TLR10 localise to the cell surface. In contrast, TLR3 and TLR7-9 are confined to intracellular compartments such as endosomes, (endo)lysosomes and endoplasmic reticulum. Differential adaptor molecules provide specific signalling pathways in different TLR family members. These pathways are described in detail in the text. Full lines indicate direct interaction. Dashed lines indicate indirect linkage. Abbreviations: AP-1, activator protein-1; IC, intracellular; DAMP, damage-associated molecular pattern; IRF, interferon regulatory transcription factor; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response gene 88; NF-kB, nuclear factor kappa B; PAMP, pathogen-associated molecular pattern; TAK, TGF-β-activating kinase; TLR, toll-like receptor; TRAF, TNFR-associated factor; TRIF, TIR-domain-containing adaptor protein-inducing interferon-β.

Supplementary Table 1 | Overview of the cellular location, PAMPs, DAMPs and synthetic ligands of the different human Toll-like receptors.

Receptor	Cellular location	Ligand: PAMP	PAMP-related pathogens	Ligand: DAMP	Synthetic ligand
TLR1	Cell surface(88, 188)	Peptidoglycan(9) Triacylated lipoproteins (TLR1/TR2 heterodimer)(36, 50, 207)	Bacteria (primarily gram-positive)	β-defensin(63)	Pam_3Cys, Pam_3CSK_4
TLR2	Cell surface(88, 188)	Lipoproteins, peptidoglycan, lipoteichoic acid, zymosan, mannan, hemagglutinin protein, glycosylphosphatidylinositol anchors, Leptospiral LPS, phenol-soluble modulin, porins(13, 15, 21, 69, 74, 88, 113, 200) Diacylated lipoproteins (TLR2/TLR6 heterodimer)(36, 50)	Bacteria (primarily gram-positive, including mycobacteria), fungi, *Measles morbillivirus, Trypanosoma cruzi, Leptospira interrogans*	Free fatty acids, HSP60, HSP70, Gp96, HMGB1, fibronectin, hyaluronan, biglycan, galectin-3, decorin, peroxiredoxins, β-defensin, uric acid, MSU crystal, PAUF, AGE-LDL, versican, EDN(7, 9, 30, 33, 63, 93, 140, 152, 162, 164, 166, 191, 192, 205, 211)	Pam_3Cys, Pam_3CSK_4, MALP-2 (TLR2/TLR6 heterodimer)
TLR3	IC compartments(88, 188)	Double-stranded RNA(69, 88)	Virus (both RNA and DNA)(188)	Self- RNAs (including mRNA and small interfering RNA), angiotensin II(9, 88, 171)	Poly (I:C)
TLR4	Cell surface(88, 188)	LPS, fusion protein, mannan, RSV protein F, MMTV and MMLV envelope proteins, VSV glycoprotein G, DENV NS1, EBOV glycoprotein(6, 69, 134, 148, 207)	Bacteria (gram-negative), virus, fungi	Free fatty acids, HSP22, HSP60, HSP70, HSP72, Gp96, HMGB1, fibronectin, hyaluronan (including lower molecular weight fragments), biglycan, galectin-3, decorin, peroxiredoxins, β-defensin, uric acid, MSU crystal, PAUF, AGE-LDL, heparan sulfate, heme, s-100 proteins (including calprotectin), fibrinogen, tenascin C, α-crystallin, surfactant protein, mmLDL, cardiolipin, serum amyloid A 3, fetuin-A, resistin, granulysin, peroxiredoxin 1, angiotensin II, ceramide, MRP 8/14(7, 9, 14, 29, 30, 33, 44, 55, 70, 72, 79, 93, 122, 138, 140, 143, 151, 157, 162, 164, 166, 171, 184, 185, 191, 192, 195, 211, 215) Oxidised LDL, amyloid-β (TLR4/TLR6 heterodimer)(85, 179)	LPS, lipid derivatives(9) Paclitaxel(196)
TLR5	Cell surface(88, 188)	Flagellin(69)	Bacteria		
TLR6	Cell surface(88, 188)	Lipoteichoic acid	Bacteria (gram-positive)	Versican(9)	MALP-2 (TLR2/TLR6 heterodimer)
TLR7	IC compartments(88, 188)	Single-stranded RNA(69, 130)	Virus, RNA from *Streptococcus* B bacteria(88)	Self-RNA, microRNA(202)	Imidazoquinoline, bropirimine, guanine analogs(9, 102)
TLR8	IC compartments(88, 188)	Single-stranded RNA(69)	Virus	Self-RNA	Imidazoquinoline(9)
TLR9	IC compartments(88, 188)	Unmethylated CpG DNA, hemozoin(60, 69, 88, 137)	Virus, bacteria, *Plasmodium falciparum*	Self-DNA (including mitochondrial DNA), HMGB1, chromatin-IgG complexes, interferon-α (30, 100, 197)	CpG ODN(9)
TLR10	Cell surface(88, 188)	No clearly defined ligand	*Listeria monocytogenes*, influenza virus A, HIV-1(9, 78, 88)		

Abbreviations: AGE-LDL, advanced glycation end-products modified low density lipoprotein; DAMP, damage-associated molecular pattern; DENV, dengue virus; EBOV, Ebola virus; EDN, eosinophil-derived neurotoxin; HMGB1, high mobility group box 1 protein; HSP, heat shock protein; IC compartments, intracellular compartments (endosomes, lysosomes, endoplasmic reticulum); IgG, immunoglobulin G; LPS, lipopolysaccharide; MALP-2, macrophage-activating lipopeptide-2; mmLDL, minimally modified low-density lipoprotein; MMLV, Moloney murine leukemia virus; MMTV, mouse mammary tumour virus; mRNA, messenger RNA; MRP, myeloid-related protein; MSU, monosodium urate; NS1, non-structural protein 1; ODN, oligodeoxynucleotides; PAMP, pathogen-associated molecular pattern; PAUF, pancreatic adenocarcinoma upregulated factor; poly(I:C), polyinosinic:polycytidylic acid; RSV, respiratory syncytial virus; TLR, toll-like receptor; VSV, vesicular stomatitis virus.

Supplementary Table 2 | Summary of the characteristics of the articles investigating the effects of acute resistance exercise.

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Fernandez-Gonzalo, 2012(51)	Moderately active undergraduate male students – n=12 – 22.1 (SE 0.5) years	Moderately active undergraduate male students – n=8 – 22.7 (SE 0.4) years	- Exercise bout (week 0), followed by an eccentric training program and repetition of the exercise bout (week 9) - CG: no training program - Exercise bout: 12 sets of 10 repetitions of the negative phase of the barbell squat at 60% MVIC - Training program: 3 sessions/week for 6 weeks - Session: 3-5 sets of 10 repetitions of eccentric barbell squat at 40-50% MVIC	Venous blood – pre, past and 2h after exercise bout	qPCR (CD14, TLR4, TNF-α) Western blot (TLR4, TRAF6, TNF-α, CD14, p65, pIκB, pIKK, TRIF, MyD88, pERK-1/2)	TLR4 mRNA: ↑ post and 2h after both bouts in both groups TLR4 protein: ↑ post and 2h after first bout in both groups; ↓2h after second bout in trained group (↔ ↑ post and 2h after second bout in CG)	CD14 mRNA: ↑ post and 2h after both bouts in both groups CD14 protein: ↑ post and 2h after first bout in both groups; ↓ 2h after second bout in trained group (↔ ↑ post and 2h after second bout in CG) TNF-α mRNA and protein: ↑ post and 2h after first bout in both groups; = in trained group after second bout (↔ ↑ post and 2h after exercise bout in CG) MyD88, TRAF6, TRIF, pIKK, pIκB, p65 protein and pERK-1/2 protein: ↑ post and 2h after first bout in both groups; = after second bout in trained group (except for ↑ pIKK post exercise and ↑ p65 2h after exercise)(↔ ↑ post and 2h after exercise bout in CG)
Fernandez-Gonzalo, 2014(52)	Healthy active (3-5h of recreational activity per week) undergraduate female students – n=12 – 22.5 (SEM 0.3) years	Healthy active (3-5h of recreational activity per week) undergraduate female students – n=8 – 22.5 (SEM 2.3) years	- Exercise bout (week 0), followed by an eccentric training program and repetition of the exercise bout (week 9) - CG: no training program - Exercise bout: 12 sets of 10 repetitions of the negative phase of the barbell squat at 60% MVIC - Training program: 3 sessions/week for 6 weeks - Session: 3-5 sets of 10 repetitions of eccentric barbell squat at 40-50% MVIC	Venous blood – pre, post and 2h after exercise bout	qPCR of PBMC (CD14, TLR4, TRAF6) Western blot (CD14, TLR4, MyD88, p65, pERK, TBK1, IRF3, TNF-α, TRAF6, TRIF, IKK, pIKK, pIκB, pIRF3, p38, pP38)	TLR4 mRNA: ↑ post and 2h after both bouts in both groups TLR4 protein: ↑ post and 2h after first bout in both groups; = after second bout in trained group (↔ ↑ post and 2h after second bout in CG)	Cell counts: no changes PBMC subpopulations CD14 and TRAF6 mRNA: ↑ post and 2h after both bout in both groups CD14 and TRAF6 protein: ↑ post and 2h after first bout in both groups; = after second bout in trained group (↔ ↑ post and 2h after second bout in CG) MyD88, TRIF, pIκB, IKK, p65 and pERK and TNF-α protein: ↑ post and 2h after first both in both groups; = after second bout in trained group (↔ ↑ post and 2h after second bout in CG) pIRF3 protein: =
Flynn, 2003(58)	Apparently healthy resistive-trained women: - taking traditional HRT – n=9 – 74.02 (SD 5.62) years - non-HRT – n=6 – 74.60 (SD 6.47) years - no hormones but medications known to influence bone – n=7 – 72.01 (SD 7.46) years	Apparently healthy sedentary women not taking hormones – n=6 – 74.20 (SD 6.98) years	- Training program with single exercise bout 1 week after last training session - CG: acclimatisation sessions, followed by normal activities - Week 0: 3 acclimatisation sessions - Week 1-10: 3 sessions/week of three sets of 10 upper and lower body exercises - Exercise bout: 10 min treadmill warm-up, three sets of 10 resistive exercises at 80% 1RM	Venous blood – pre, post and 2h after exercise bout (or after rest for CG)	qPCR (TLR4, CD14, IL-6, TNF-α, IL-1β) Whole blood stimulation with LPS (24h) with ELISA	TLR4 mRNA: collapsed over time ↓ in trained groups compared to CG (no significant time differences) TLR4 mRNA/monocyte: ↑ in CG compared to trained group at all time points	Leukocyte count: ↑ post exercise in trained groups with normalisation at 2h (↔ CG =) Mononuclear cell count: ↑ post exercise in HRT and non-HRT with normalisation at 2h (↔ CG and medication with bone influence =) Monocyte count: ↑ post exercise in trained groups with normalisation at 2h (↔ CG ↓ post exercise with normalisation at 2h) CD14 mRNA: collapsed over time ↓ in trained compared to CG CD14 mRNA/monocyte: ↑ in CG compared to trained groups at all time points IL-6 and IL-1β mRNA: no significant differences TNF-α mRNA: collapsed over time ↑ in CG compared to trained groups LPS-stimulation: ↓IL-6, TNF-α in trained groups; IL-1β =

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
McFarlin, 2004(116)	Elderly (≥ 10 years postmenopausal) trained (≥ 72 exercise sessions in the last 6 months) women – n=10 – 67 (SD 5) years	Elderly (≥ 10 years postmenopausal) untrained women – n=10 – 69 (SD 5) years	- Single exercise bout (exercise & control group) - Upper and lower body exercise: 3 sets, 9 exercises, 10 repetitions at 80% of 1RM	Venous blood – pre, post and 2h, 6h and 24h after exercise	Flow cytometry (CD14, TLR4) qPCR (CD14, TLR4, IL-6, TNF-α, IL-1β) Whole blood stimulation with LPS (24h) with ELISA	$CD14^+$ monocyte TLR4: untrained ↑ compared to trained (group averages), no time factor	Cell count: no group factor Total leukocytes: post-exercise ↑ compared to pre-exercise and 24h; at 6h ↑ compared to pre-exercise $CD14^+$ count: at 6h ↑ compared to 2h and 24h; at post-exercise ↑ compared to 2h LPS-stimulated cytokines: IL-6, IL-1β, TNF-α concentration at 6h ↑ than other time points; IL-6 post-exercise ↑ than at 2h Gene expression: no significant results
Age is given as mean unless otherwise stated. Abbreviations: 1RM, one-repetition maximum; CD, cluster of differentiation; CG, control group; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal-regulated protein kinase; h, hour; HRT, hormone replacement therapy; IFN, interferon; IKK, IκB kinases; IL, interleukine; IRF, interferon regulatory transcription factor; LPS, lipopolysaccharide; min, minute; mRNA, messenger RNA; MVIC, maximal voluntary isometric contraction; MyD88, myeloid differentiation primary response gene 88; PBMC, peripheral blood mononuclear cells; qPCR, quantitative polymerase chain reaction; SD, standard deviation; SE, standard error; SEM, standard error of the mean; TBK, TANK-binding kinase; TNF, tumor necrosis factor; TLR, toll-like receptor; TRAF, TNFR-associated factor; TRIF, TIR-domain-containing adaptor protein-inducing interferon-β.							

Supplementary Table 3 | Summary of the characteristics of the articles investigating the effects of acute aerobic exercise.

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Bergman, 2016(12)	- Obese sedentary (<2h physical activity/week) individuals – n=14 (9 ♂, 5 ♀) – 39.7 (1.6) years - T2DM – n=15 (11 ♂, 4 ♀) – 42.5 (1.1) years - Endurance-trained athletes (average training 12.3h/week) – n=15 (11 ♂, 4 ♀) – 41.3 (0.86) years	/	- Single exercise bout - Cycling: 1.5h at 50% VO_2max	Venous blood – pre, during last 30 min of exercise and during last 30 min of recovery Muscle biopsy quadriceps femoris – pre, post and 2h after exercise	NEFA kit (NEFA) Western blot of muscle tissue (TLR4, JNK, MAP4K4, ERK1/2, Akt)	TLR4 = (no differences between groups or after exercise)	Serum TNF-α: ↑ after exercise with normalisation after recovery Baseline serum NEFAs: total concentration = between groups; palmitic acid and stearic acid ↑ in T2DM than athletes or obese; arachidic acid ↑ in T2DM compared to obese; eicosapentaenoic acid ↑ in obese than T2DM or athletes; erucic acid ↑ in athletes than in obese or T2DM Serum NEFAs after exercise: ↑ after exercise with further increase during recovery in all groups $JNK^{Thr138/185}$ phosphorylation/total JNK: ↓ in athletes compared to T2DM and obese at baseline; ↑ after exercise in all groups with normalisation after recovery MAP4K4, ERK1/2 phosphorylation/total ERK1/2: no differences between groups or after exercise Akt^{Ser473} phosphorylation/total Akt: ↑ in athletes compared to T2DM or obese at baseline; no impact of exercise

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Booth, 2010(17)	Trained cyclists – n=8 (5 ♂, 3 ♀) - 32.1 (SD 4.2) years)	/	- Single exercise bout - Cycling: 60 km in fastest time possible (mean completion time 92.1 min, mean HR 83% age-predicted MHR)	Venous blood – pre, post and 1h after exercise	Flow cytometry (CD14, CD16, TLR2, TLR4, HLA-DR) Serum stimulation assay of pre-exercise PMBC with flow cytometry	↑ TLR2, TLR4 post and after 1h TLR2 on monocyte subsets: ↑ TLR2 on $CD14^{++}/CD16^{+}$ after exercise, no other exercise effects TLR4 on monocyte subsets: ↑ TLR4 on $CD14^{++}/CD16^{+}$ after 1h, no other exercise effects Serum exposure: TLR2, TLR4 =	Cell count: ↑ total leukocyte, neutrophil, lymphocyte and monocyte count post exercise; ↑ leukocyte, neutrophil and monocyte count after 1h with normalisation of lymphocyte count Monocyte subsets: ↑ $CD14^{++}/CD16^{-}$, $CD14^{+}/CD16^{++}$, $CD14^{++}/CD16^{+}$ post exercise with normalisation after 1h; ↓ proportion $CD14^{++}/CD16$ and ↑ proportion $CD14^{+}/CD16^{++}$ and $CD14^{++}/CD16^{+}$ with normalisation after 1h Monocyte HLA-DR: ↓ post and after 1h Serum exposure: ↑ HLA-DR on $CD14^{+}/CD16^{++}$ cells with 1h post-exercise serum compared to resting serum
Capó, 2014(22) and Capó, 2016(23)	*Male soccer players from the Real Mallorca B team – n=9 – 20.4 (SEM 0.5) years (not considered in this review)*	Male soccer players from the Real Mallorca B team – n=6 – 19.3 (SEM 0.4) years	- Training program with single exercise bout, with docosahexanoic acid or placebo supplementation (5 days/week) throughout the season *(docosahexanoic acid supplementation group not considered in this review)* - CG: placebo supplementation, training program and exercise bout - Training program: 8 weeks of physical activity related to football training season - Single exercise bout: 2h of habitual physical activity (15 min warm-up, Leger Boucher test, 15 min recovery exercise, small-sided games, 20 min soccer match)	Venous blood – at the beginning and end of the nutritional intervention and 2h after the exercise	Capó, 2014 Flow cytometry (cell counts) Chromatography (fatty acids) PBMC stimulation with LPS (2h) with Biochip array Biochip array (GMCSF, MIP1α, MCP1, IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-15, TNF-β, IFN-γ ELISA (IL-8, TNF-α) Western blot of PBMC (TLR4) Capó, 2016 PBMC stimulation with LPS (2h)(37°C and 39°C) with ELISA Randox Biochip Array (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α)	TLR4 = after program; ↑ TLR4 after acute exercise	Capó, 2014 Fatty acid composition of erythrocytes: ↓ proportion C20:2 after program compared to baseline Cell count: ↑ proportion basophils after program; leukocytes =; ↑ proportion monocytes and ↓ proportion lymphocytes and basophils after acute exercise Plasma cytokines and growth factors: = after program; ↑ IL-6 after acute exercise PBMC stimulation: ↑IL-6 and TNF-α after exercise Capó, 2016 LPS-stimulated PBMC: ↑ IL-1β, IL-6, IL-8 in 39°C compared to 37°C; ↓ IL-2 in 39°C compared to 37°C LPS-stimulated PBMC: = (when expressed per blood or per monocyte); ↑ IL-1α, IL-1β, IL-4, IL-6, IL-8, IFN-γ and TNF-α after acute exercise; ↓ IL-2 after acute exercise
Capó, 2016(24)	Young and senior male taekwondo athletes (physical activity of 1-2h daily 5-7 days per week) - young: n=10 – 22.8 (SEM 3.8) years - senior: n=8 – 45.6 (SEM 1.6) years	/	- Single exercise bout before and after 5 weeks of nutritional intervention *(test after intervention was not included in this review)* - Treadmill: incremental maximal test until exhaustion (71.84 min for senior group, 72.02 min for young group)	Venous blood – pre and 1h after exercise	Enzymatic Wako kit (NEFA) ELISA (IL-6, TNF-α, NF-κB p50) qPCR (TLR2, TLR4, NF-κB, 5-LOX, 15-LOX2, IL-1β, IL-8, IL-10, IL-15, TNF-α, HSP70)	TLR2, TLR4 =	Plasma NEFA: ↑ in young and old athletes after exercise Plasma IL-6, NF- κB p50, TNF-α and HSP70: no impact of exercise in young and old group Gene expression: no group differences or impact of exercise
Durrer, 2017(43)	T2DM patients with HbA1c <8% – n=10 (5 ♂, 5 ♀) – 57.9 (SD 5.4) years	Age-matched normoglycemic controls completing 150-300 min of light-moderate physical activity per week (self-reported) – n=9 (4 ♂, 5 ♀) – 55.8 (SD 9.0) years	- Single exercise bout of HIIT (patient & control group) - Cycling: 7 times 1 min at 85% of maximal aerobic power output, separated by 1 min of recovery	Venous blood – pre, post and 1h after exercise	MagPix (plasma TNF-α) Flow cytometry (CD14, CD16, TLR2, TLR4) Whole blood stimulation with LPS (4h) with MagPix assay	TLR2 expression on classical and $CD16^{+}$ monocytes: ↓ post and 1h after exercise TLR2 expression on $CD16^{+}$ neutrophils: ↑ in T2DM compared to CG; no effect of exercise TLR4 expression on classical monocytes: no effect of time or group TLR4 on $CD16^{+}$ monocytes and neutrophils: ↑ in T2DM compared to CG; no effect of exercise	Cell count: ↑ total leukocytes, classical monocytes and $CD16^{+}$ monocytes post exercise with normalisation after 1h; proportion $CD16^{+}$ monocytes = Plasma TNF-α: ↓ at 1h compared to pre exercise in T2DM and CG LPS-stimulated blood culture: absolute TNF-α concentration ↓ at 1h post-exercise compared to pre and post exercise; when corrected for leukocyte number ↓ at 1h compared to pre exercise and ↓ overall in T2DM compared to CG

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Falgiano, 2018(48)	Healthy, recreationally active participants – n=8 (6 ♂, 2 ♀) – 19 (SEM 1) years	/	- Single exercise bout with and without preceding curcumin supplementation (average washout period of 38 days)*(test with preceding supplementation is not considered in this review)* - Running: 60 min at 65% VO_2max in 37°C and 25% RH	Venous blood – pre, post, 1h and 4h after exercise	Western blot of PBMC (TLR4, pAMPKα1, p-HSF1, HSP70, pIκBα, IκBα, MyD88, pNF-κB p65, NF-κB p65, SIRT1)	↓TLR4 1h after exercise with normalisation at 4h	MyD88 protein: = pIκB/IκB and pNF-κB/NF-κB ratio: pIκB/IκB =; ↑ pNF-κB/NF-κB at 1h after exercise p-HSF1 and HSP70: p-HSF1 =; ↓HSP70 at 1h compared to 4h after exercise pAMPK and SIRT1: ↓5 pAMPK and SIRT1 1h after exercise
Fuller, 2018(62)	Healthy male participants – n=12 – 23 (SEM 1) years	/	- Consumption high-fat meal (1000 kcal and 57% fat) with and without single exercise bout on preceding day (separated by 4-7 days) - Cycling: 45 min at 65% VO_2peak	Venous blood – pre, and 0.5, 1, 2, 3 and 4h after the high-fat meal	Enzymatic assay (NEFA) Western blot of PBMC (4h after meal consumption)(TRL4, MyD88)	TLR4: = (no impact of high-fat meal or exercise)	Plasma NEFA: high-fat meal (with or without prior exercise) decreased plasma NEFA MyD88: no impact of high-fat meal or exercise
Gleeson, 2006(69)	Endurance-trained male cyclists – n=11 – 20 (SD 2) years)	/	- Single exercise bout - Cycling: 2.5h at 60% VO_2max in 20°C and 40% RH	Venous blood – pre, post and 1h after exercise	Flow cytometry (TLR1, TLR2, TLR3, TLR4)	TLR on $CD14^+$ monocytes post: TLR1, TLR3, TLR4 =; ↓ TLR2 TLR on $CD14^+$ monocytes 1h after: ↓ TLR1, TLR2, TLR3, TLR4	Core temperature: =
Keech, 2016(89)	CFS patients with 1.2h (SD 1) of at least moderate intensity exercise per week – n=10 (4 ♂, 6 ♀) – 41.4 (SD 8.4) years	Matched healthy control participants with 1.7h (SD 1.4) of at least moderate intensity exercise per week – n=12 (4 ♂, 8 ♀)(one subject did not provide blood) – 34.1 (10.2) years	- Single exercise bout (patient & control group) - Cycling: 25 min at 70% age-predicted MHR	Venous blood – 24h pre, post and 1, 4, 24 and 72h after exercise	qPCR of PBMC (IL-1β, IL-6, IL-10, IFN-γ, CD14, TLR4)	TLR4 =	Gene expression: no significant effect of exercise on any gene
Lackermair, 2017(92)	*Male volunteers with a history of ≥1 finished half marathon – n=42 – 40.8 (SD 9) years (not considered in this review)*	Male volunteers with a history of ≥1 finished half marathon – n=58 – 41 (SD 9.5) years	- Regular training (54 km/week on average) for 4 weeks, accompanied by *nonalcoholic beer (1-1.5L/day)(not considered in this review)* or placebo supplementation, followed by a single exercise bout - CG: placebo supplementation, regular training and marathon race - Single exercise bout: marathon race (227 min on average)	Venous blood – at inclusion, in the week before the marathon (after 3 weeks of beverage consumption and training) and 1h, 24h and 72h after finishing	Flow cytometry (leukocyte subsets) qPCR of PBMC (TLR7)	↑TLR7 after training; ↓ TLR7 1h after marathon with ↑ after 24h and ↓ after 72h	mDC: = after training; ↑ after marathon, with partial normalisation after 24h and complete normalisation after 72h pDC: ↑ after training; ↓ after marathon with recovery after 24h
Lancaster, 2005(96)	Healthy moderate-to-well endurance-trained male subjects – n=11 – 25 (SEM 1) years	/	- Single exercise bout - Cycling: 5 min at 40% Wmax, followed by 1.5h at 55% Wmax (~ 65% VO_2max) in 34°C and 30% RH	Venous blood – pre, post and 2h after exercise	Flow cytometry (CD14, TLR1, TLR2, TLR4, TLR9, HLA-DR, CD80, CD86, IL-6) Whole blood stimulation (6 or 24h) with zymosan (TLR2), LPS (TLR4) and poly(I:C) (TLR3) with flow cytometry	Post exercise and after 2h: ↓ $CD14^+$ monocyte TLR1, TLR2, TLR4; TLR9 =	Unstimulated exercise samples: $CD14^+$ monocyte CD86 ↓ and MHC II ↓ 6h stimulated exercise samples: upregulation $CD14^+$ monocyte CD86 and MHC II ↓ compared to resting samples 24h stimulated exercise samples: upregulation $CD14^+$ monocyte CD80 = between rest and exercise 6h LPS-stimulated sample: $CD14^+$ intracellular IL-6 upregulation ↓ compared to resting samples 6h zymosan-stimulated sample: $CD14^+$ intracellular IL-6 upregulation ↑ compared to resting samples

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Lansford, 2016(99)	Healthy, non-smoking recreationally active subjects: - male – n=16 – 24.5 (SEM 0.8) year - female – n=10 – 22.40 (SEM 0.52) years	/	- Single exercise bout - Cycling: 60-70% VO_2peak until reaching total energy expenditure of 2.5 MJ (43.6 min on average in men, 62.7 min on average in female)	Venous blood – pre and post exercise	FACS qPCR (TLR2, TLR4, IL-6R)(male subjects only)	TLR2 expression: ↑ in $CD62E^+$ PBMC at baseline; ↓ in $CD62E^+$ cells after exercise TLR4 expression: ↓ in $CD31^+$ PBMCs compared with $CD34^+$ and $CD62E^+$; no impact of exercise	Circulating angiogenic cells: ↓ $CD14^+/CD31^+$ cells after exercise (men only); no change $CD34^+/VEGFR2^+$ or $CD3^+/CD31^+$ cells Microparticles: ↑ $CD62E^+$ endothelial microparticles after exercise in men (↔ = in women); no change $CD31^+/CD42b^-$ endothelial microparticles; lower baseline $CD34^+$ microparticles in women with ↑ after exercise (↔ = in men) IL-6R expression: ↓ in $CD31^+$ PBMCs compared with $CD34^+$ and $CD62E^+$; no impact of exercise
Light, 2009(106)	CFS patients – n=19 (4 ♂, 15 ♀) – 42.2 (SE 2.7) years	Control subjects – n=15 (5 ♂, 10 ♀) – 35.6 (SE 3.0) years	- Single exercise bout (patient & control group) - Combined arm-leg ergometer: 25 min at 70% age-predicted MHR	Venous blood – pre and 0.5, 8, 24 and 48h after exercise	qPCR (IL-6, IL-10, TLR4, TNF-α, CD14))	TLR4 mRNA: baseline =; ↑ AUC for all time points post-exercise in patient group (↔ CG =) Post-exercise fitness-matched subgroups: TLR4 mRNA =	BMI: higher in CFS patients Total leukocyte count: ↑ at 8h with normalisation after 24 and 48h, no group differences Baseline: IL-6, IL-10, TNF-α, CD14 = between groups Post-exercise: non-significant higher values for IL-6, TNF-α and CD14 across all time points in the CFS group; significantly elevated AUC for all time points for IL-10
Millard, 2013(121)	Healthy volunteers accustomed to exercise – n=29 (19 ♂, 10 ♀) – age range 25-45 years	/	- Single exercise bout - Stairclimbing: up and down 150 stairsteps (duration on average 68.8 s)	Venous blood – pre and post exercise	Flow cytometry (TLR2)(n ≥5) Stimulation of NK cell culture with recombinant human IL-2, IL-12 or LTA and Pam3CSK4 Stimulation of NK cell culture with IL-2/IL-12 or LTA and Pam3CSK4 with MACS cytokine secretion assay Stimulation of NK cell culture with IL-2 (48h) with ELISA (IFN-γ secretion) Stimulation of NK cell culture for degranulation with IL2/IL-12 (overnight) with flow cytometry ^{51}Cr-release assay of freshly isolated or IL-2 activated NK cells (n=5)	$TLR2$ on $CD56^{pos}$, $CD56b^{right}$ or $CD56^{dim}$ NK cells: =	Cell count: ↑PBMC, NK cells after exercise; ↓ proportion of $CD56^{bright}/CD16^{neg/dim}$ in total $CD56^{pos}/CD3^{neg}$ NK population after exercise NK cell IFN-γ secretion, degranulation and cytotoxicity without exogenous stimulation: slight ↓ degranulating NK cells after exercise, no other effects Cytokine stimulated NK cells: IL-2 stimulation at pre-exercise ↑IFN-γ after 4h and 24h (↔ = after exercise); intracellular IFN-γ production similar before and after exercise; ↓ degranulation after exercise; after 5 days of IL-2 stimulation ↓ cytotoxicity of post-exercise NK cells TLR2-stimulated NK cells (similar TLR2 expression of the samples): ↓ frequency IFN-γ-secreting cells after exercise
Neubauer, 2013(128)	Healthy male endurance athletes – n=8 – 25.0 (SD 4.1) years	/	- Training program (6 weeks of endurance exercise, including cycle to run transition training) followed by a single exercise bout - Single exercise bout: 60 min intense cycling at 105% of power output attained at gas exchange threshold, followed by 60 min of intense running at 10-km time trial pace	Venous blood – 1 week before and 3, 48 and 96h after the exercise bout (prior 48h abstinence from exercise)	ELISA (HSP70, IL-1β, IL-1ra, IL-6, IL-10) Microarray gene expression analysis qPCR (IL-1R1, IL-1ra, IRAK3, TLR4)	↑ TLR4 at 3h with normalisation after 48h	Cell count: ↑ total leukocytes and neutrophils at 3h with normalisation after 48h Plasma HSP70: = Plasma cytokines: ↑ IL-1ra, IL-6, IL-10 at 3h; IL-1β =; all values normalised at 48h Microarray analysis: ↑ KEGG TLR signalling pathway at 3h, with normalisation after 48h qPCR: ↑IL-1R1, IL-1ra, IRAK3 at 3h with normalisation after 48h

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Nickel, 2012(129)	See "Nickel *et al.* 2011" in Supplementary Table 5		- Single exercise bout - Running : marathon race (263 min obese non-elite (ONE), 235 min lean non-elite (LNE), 217 min elite (LE))	Venous blood – 2-5 days pre (no exercise in preceding 2 days), post and 24h after marathon	ELISA (serum IL-6, IL-10, TNF-α) Flow cytometry qPCR of PBMC (TLR2, TLR4, TLR7) Western blot of PBMC (TLR2, TLR4, TLR7)	TLR2 mRNA and protein: = (no differences between groups or after exercise) TLR4 mRNA and protein: ↓ mRNA post marathon in LNE; ↑ mRNA 24h after marathon compared to baseline in all groups; protein = TLR7 mRNA and protein: ↓ mRNA post marathon in all groups; ↑ mRNA 24h after marathon compared to baseline in all groups; protein ↓ 24h after marathon in all groups	Myeloid DCs: baseline =; ↑ post marathon with normalisation after 24h, except for ONE with persistent increase Plasmacytoid DCs: baseline =; ↓ post marathon with normalisation after 24h, except for LNE with24h values lower than baseline Serum IL-6: ↓ in LE at baseline; ↑ post and 24h after marathon in all groups Serum TNF-α: baseline =; ↑24h after marathon in all groups Serum IL-10: ↓ in ONE at baseline; ↑ post marathon with normalisation after 24h in all groups
Oliveira, 2010(136)	Healthy endurance-trained men – n=9 – 25 (SD 5) years	Healthy endurance-trained men – n=6 – 25 (SD 2) years	- Three exercise bouts (2 preliminary and 1 main trial separated by ≥ 1 week) - CG: remain seated during trials - Cycling: 1.5h at 75% VO_2peak	Venous blood – pre, post and 1,4 and 24h after exercise (CG: pre and after 1.5 and 2.5h)	Flow cytometry (TLR2, TLR4, CD14)	Monocyte TLR2: = Monocyte TLR4: ↓ post and 1h after with normalisation after 4h (↔ CG =)	Leukocyte count: ↑ total leukocyte and monocyte count post, 1h and 4h post-exercise with normalisation after 24h
Perandini, 2016(141)	Physically inactive (≥6 months physical inactivity) women with SLE: - patients with active SLE (SLE_{active}) – n=4 – 32.5 (SD 3.4) years - patients with inactive SLE ($SLE_{inactive}$) – n=4 – 34.5 (SD 3.4) years	Age- and BMI-matched healthy control women – n=4 – 29.3 (SD 4.8) years	- Single exercise bout (patient & control group) - Treadmill: 5 min warm-up, followed by 30 min at predetermined intensity (50% of difference between ventilator anaerobic threshold and respiratory compensation point)	Venous blood – pre, post and 3h after exercise	qPCR array of leukocytes	Healthy control: ↓TLR3, TLR7 post exercise with normalisation at 3h; ↑ TLR1, TLR8 at 3h after exercise SLE_{active}: ↓ TLR3, TLR6 post exercise with normalisation at 3h after exercise; ↑ TLR7, TLR9 at 3h; ↓ TLR4, TLR8 at 3h after exercise $SLE_{inactive}$: ↑ TLR3 at 3h after exercise	Healthy control: ↓ MyD88, IRF3, TNF, IL-1α, IL-2,IL-4, IL-6, IL-10, IL-17A, IL-18 and CD80 post exercise with normalisation after recovery; ↓ IL-23A, IL-5 and IL-13 post exercise with increased expression at recovery; no change post exercise but ↑ expression at recovery of CD14, IL-1β, IL-1R1 and MAPK8 SLE_{active}: ↓ IL-5, IL-17A and IL-18 post exercise with normalisation after recovery; ↑ CD14 and IRF7 post exercise with normalisation after recovery; ↓ IL-1α, IL2, IL-4, IL-6, IL-10, IL-13 and IFN-γ post exercise with ↑ expression after recovery $SLE_{inactive}$: ↓ IFN-γ, IL-2, IL-5, IL-10, IL-13, IL-17A and IL-18 post exercise with normalisation after recovery; ↓ CD80, IL-4 and IL-6 post exercise with ↑ expression after recovery; ↑ IRF7 post exercise and after recovery; no change at baseline but ↑ MAPK8 at 3h after exercise
Radom-Aizik, 2014(146)	Healthy young men (no elite athletes or subjects with vigorous participation in competitive sports) – n=12 – 26 (SE 0.6) years	/	- Single (intermittent) exercise bout - Cycling: ten 2-min. bouts at 82% VO_2max, with 1-min rest interval between each bout	Venous blood – pre and post exercise	Flow cytometry (CD14, CD16) Gene expression microarray of monocytes qPCR (TNF, HSPA1A, HSPA8, TLR4)	↓ TLR4	Cell count: ↑ classical and non-classical monocyte number post exercise; ↑ proportion non-classical monocytes post exercise Gene expression microarray: alteration of MAPK signalling pathway after exercise qPCR: ↑ HSPA1A, HSPA8 post exercise; ↓TNF post exercise

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Simpson, 2009(170)	Moderately trained male subjects – n=15 – 26.4 (SD 6.7) years	/	- Single exercise bout - Treadmill: 45 min at 75% VO_2max	Venous blood – pre, post and 1h after exercise	Flow cytometry (CD14, CD16, TLR2, TLR4, HLA-DR)	Post exercise: $CD14^+$ monocyte TLR2 = ; $CD14^+/CD16^+$ monocyte TLR2 ↓ (~ $CD14^{++}/CD16^+$ monocytes); monocyte TLR4 = After 1h: monocyte TLR2 = (compared to baseline; $CD14^+$ monocyte TLR4 ↓ (~ $CD14^+/CD16^-$ monocytes); $CD14^+/CD16^+$ monocyte TLR4 ↑(~ $CD14^+/CD16^{++}$ monocytes)	Difference TLR2, TLR4 and HLA-DR expression between subsets not affected by exercise Post exercise: ↑ proportion $CD14^+/CD16^+$ within $CD14^+$ monocyte population After 1h: ↑ proportion $CD14^+/CD16^+$ monocytes within $CD14^+$ monocyte After 1h: $CD14^+$ monocyte HLA-DR ↓ (~ $CD14^+/CD16^-$ and $CD14^{++}/CD16^+$ monocytes)
Slusher, 2018(173)	Healthy male participants – 24.2 (SD 4.0) years: - aerobically trained(≥150 min of moderate-to-vigorous aerobic exercise/week) – n=12 - aerobically untrained (<150 min of any moderate-to-vigorous physical activity/week – n=13	/	- Single exercise bout - Treadmill: maximal oxygen consumption until voluntary exhaustion (798.24 s on average)	Venous blood – pre and post exercise	Flow cytometry (CD14, CD16, TLR4) PBMC stimulation with LPS (24h) with ELISA	Monocyte TLR4: ↓ on total monocyte population, classical and intermediate monocytes	Cell count: proportion monocytes of PBMC = Monocyte subpopulations: ↓ classical monocytes; ↑ intermediate and non-classical monocytes CD14 expression: ↓ on total monocytes and all subpopulations CD16 expression: ↑ on intermediate monocytes (but still lower than non-classical monocytes) LPS-stimulated cytokines: ↓IL-6 and IL-10 production; ↑ IL-6/IL-10 ratio; ↑ TNF-α
Sureda, 2014(181)	Professional male divers – n=9 – 33.9 (SE 3.8) years	/	- Single exercise bout - Immersion to a depth of 50 m for a total time of 35 min, participants continuously swam while at depth	Venous blood – pre and 0.5 and 3h after exercise	qPCR of neutrophils (TLR2, TLR4, NF-κB, TNF-α, IL-1B IL-6, IL-8, IL-10, HSP72, lipoxygenase and myeloperoxidase) Colorimetric assay (MDA)	TLR2 =; ↑ TLR4 0.5h after exercise with further increase at 3h	Cell count: ↑ neutrophils after 3h compared to baseline and 0.5h after exercise MDA: = NF-κB: ↑ NF-κB 0.5h after exercise with further increase after recovery TNF-α: = IL-1B, IL-6, IL-8 and IL-10: ↑ IL-6 0.5h after exercise with further increase after recovery; ↑ IL-1B, IL-8 and IL-10 after 3h HSP72: ↑ after 3h Myeloperoxidase and lipoxygenase: myeloperoxidase =; ↑ lipoxygenase after 3h
Ulven, 2015(189)	Healthy non-smoking men – n=10 – median 25 years (range 22-28)	/	- Two test days separated by 1 week (data are calculated as average of the 2 test days) - Cycling: 1h at 70% VO_2max	Venous blood – pre and post exercise	ELISA (TNF-α, IL-6, IL-10) qPCR of PBMC (IL-1β, IL-8, IL-18, TNF-α, IFN-γ, TLR2, TLR4, TLR6)	↓TLR2; TLR4, TLR6 =	Serum cytokines: ↑ TNF-α, IL-6, IL-10 Cytokine mRNA: ↑ IL-1β, IL-8; TNF-α, IFN-γ, IL-18 =
VanHaitsma, 2016(194)	Trained cyclists – n=20 (10 ♂, 10 ♀) – 36.1 (SD 9.7) years	/	- Single exercise bout under two different conditions, separated by ≥ 1 week and performed at random order - Cycling: 40 km at race effort at temperate (21°C and 20% RH)(75.2 min) and hot (35°C and 25% RH)(79.0 min) conditions	Venous blood – pre and 0.5, 8, 24 and 48 after exercise	qPCR of whole cell layer (IL-6, IL-10, TLR4)	↓ TLR4 at 0.5 and 8h after exercise in both conditions, levels remained decreased at 24h and 48h after hot conditions, but returned to baseline after temperate conditions	IL-10 mRNA: ↑ at 0.5 and 8h in both groups IL-6 mRNA: only group effect with higher IL-6 levels for exercise in hot conditions across all time points

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
White, 2012(201)	- CFS patients – n=22 (3 ♂, 19 ♀) – 40.8 (SE 2.0) years - RRMS patients with self-reported fatigue and definite MS – n=20 (2 ♂, 18 ♀) – 41.5 (SE 2.0) years	Healthy controls – n=4 (4 ♂, 19 ♀) – 38.7 (SE 2.4) years	- Single exercise bout (patient & control group) - Schwinn Air-Dyne ergometer: 30 min at 70% age-predicted MHR	Venous blood – pre and 0.5, 8, 24 and 48 after exercise	qPCR of leukocytes (CD14, TLR4, IL-6, IL-10, lymphotoxin-α)	TLR4 mRNA: baseline =; ↑ 0.5h after exercise in control; ↓ 0.5h, 8h and 48h after exercise in MS; = after exercise in CFS	CD14 mRNA: baseline =; ↑ 0.5h after exercise in all groups; ↑8h after exercise in CFS and control group; ↑24h after exercise in CFS group only; at 24h normalisation in all groups IL-6 mRNA: baseline =; ↓ 0.5h after exercise and ↑ 48h after exercise in MS IL-10 mRNA: ↓ 0.5h after exercise in control and MS group; ↑ 8h after exercise in control and MS group; ↑ 48h after exercise in CFS group Lymphotoxin-α mRNA: ↓ 0.5h after exercise in control group

Age is given as mean unless otherwise stated. Abbreviations: AMPK, 5'-AMP-actived protein kinase; AUC, area under the curve; CD, cluster of differentiation; CFS, chronic fatigue syndrome; CG, control group; DC, dendritic cell; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal-regulated protein kinase; FACS, fluorescence-activated cell sorting; GMCSF, granulocyte macrophage colony-stimulating factor; h, hour; HIIT, high-intensity interval training; HR, heart rate; HLA-DR, human leukocyte antigen – DR isotype; HSF, heat shock factor; HSP, heat shock protein; IFN, interferon; IL, interleukine; IRAK, IL-1R-associated kinase; IRF, interferon regulatory transcription factor; JNK, c-Jun N-terminal kinase; KEGG, Kyoto Encyclopedia of Genes and Genomes; LOX, lipoxygenase; LPS, lipopolysaccharide; LTA, lipoteichoic acid; MAPK, mitogen-activated protein kinase; MAP4K4, mitogen-activated protein kinase kinase kinase kinase 4; MDA, malondialdehyde; MCP, monocyte chemotactic protein; mDC, myeloid dendritic cell; MHC, major histocompatibility complex; MHR, maximal heart rate; min, minute; MIP, macrophage inflammatory protein; mRNA, messenger RNA; MS, multiple sclerosis; MyD88, myeloid differentiation primary response gene 88; NEFA, non-esterified fatty acid; NF-κB, nuclear factor kappa B; NK, natural killer; PBMC, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cell; poly(I:C), polyinosinic:polycytidylic acid; qPCR, quantitative polymerase chain reaction; ra, receptor antagonist; RH, relative humidity; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SE, standard error; SEM, standard error of the mean; SIRT, sirtuin; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor; TLR, toll-like receptor; W, power output.

Supplementary Table 4 | Summary of the characteristics of the articles investigating the effects of resistance exercise programs.

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Alfatlawi, 2019(5)	Women without experience in exercise – n=10 – 64.1 (SEM 1.1) years	Women without experience in exercise – n=10 – 69.0 (SEM 0.9) years	- Training program: 2 sessions/week for 10 weeks - CG: maintained physical activity routines - Upper and lower body exercises: 10 min warm-up, exercises at 60-80% 1RM	Venous blood – pre and post program	qPCR of peripheral blood cells (TLR4) ELISA (IL-6, IL-10)	↓ TLR4 in trained group (↔ CG =)	IL-6 and IL-10: IL-6 =; ↑ IL-10 in trained group (↔ CG =)
Cheng, 2015(34)	Patients with chief complaint of nonspecific low back pain – n=30 (15 ♂, 15 ♀) – 45 (3.25) years	/	- Training program: 3 sessions/week for 4 weeks - Session: 5 min stretching, 10 min back muscle strengthening, 5 min lower limb strengthening	Venous blood – pre and post program	ELISA (plasma IL-1β, IL-6, IL-8, TNF-α, IFN-γ) qPCR (TLR4, SIRT1 Western blot of lymphocytes (NF-κB, IκB) Enzymatic assay (superoxide dismutase, catalase, hydrogen peroxide)	↓ TLR4	SIRT1 mRNA: ↓ Plasma cytokines: ↓ IFN-γ, IL-1β, IL-6, IL-8 and TNF-α Lymphocyte NF-κB and IκB: ↓ NF-κB p65; ↑ IκB Superoxide dismutase and catalase: ↑ Hydrogen peroxide: ↓
Colleluori, 2019(40)	Obese older adults with a sedentary (regular exercise <1h/week) lifestyle and mild-to-moderate frailty: - aerobic exercise (AE) – n=11 (4 ♂, 7 ♀) – 71 (SE 1) years - resistance exercise (RE) –n=12 (6 ♂, 6 ♀) – 72 (SE 2) years - combined exercise (CE) – n=12 (6 ♂, 6 ♀) – 69 (SE 1) years	Obese older adults with a sedentary (regular exercise <1h/week) lifestyle and mild-to-moderate frailty – n=12 (4 ♂, 8 ♀) – 70 (SE 1) years	- Training program: 3 sessions/week for 26 weeks, weight management program and balanced diet with energy deficit of 500-750 kcal/day - CG: educational classes about healthful diet, no participation in exercise programs - AE: 60 min at 65-85% MHR - RE: 60 min upper and lower body exercise at 65-85% 1RM - CE: 75-90 min aerobic and resistance exercise	Vastus lateralis muscle biopsy – pre and after 6 months	Gene expression assay (IL-6, TNF-α, NF- κB, HSP704_9, TLR2)	↑ TLR2 in AE after program compared to the other groups which showed a downregulatory trend	Gene expression assay: ↑ HSP704_9 AE (↔ = in other groups); IL-6, TNF-α, NF- κB = (no difference between groups or after exercise)

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Markofski, 2014(112)	Physically inactive (≤2 days/week moderate activity in the previous 6 months and estimated VO_2peak ≤ 40th percentile for respective age) overweight or obese (BMI 25-39.9 kg/m²) adults – n=26 (9 ♂, 17 ♀) – 58.0 (SD 5.7) years: - resistance exercise (RT) – n=14 - resistance exercise and energy restriction diet (RT-ER) – n=12	Physically active (≥3 days/week moderate and/or vigorous activity in the previous 6 months and estimated VO_2peak ≥ 70th percentile for respective age) lean-to-overweight (BMI 22.4-29.9 kg/m²) adults – n=9 (6 ♂, 3 ♀) – 60.1 (SD 6.1) years	- Training program: 3 sessions/week for 12 weeks - CG: maintained level of physical activity - RT-ER: additional diet 750 kcal below energy need - Upper and lower body exercises: 5 min warm-up, 3 sets at 70-80% 1RM or more	Venous blood – pre and post program	Flow cytometry (CD14, CD16, TLR4) Whole blood stimulation with LPS with or without polymyxin B (24h) with ELISA	TLR4 = (no group differences, no impact of intervention)	Cell count: $CD14^+/CD16^+$ monocyte proportion ↑ in physically inactive (and more specifically obese) subjects at baseline; after intervention ↓ in RT group (more specifically overweight subgroup) and = in RT-ER group LPS-stimulated TNF-α: no group or intervention differences LPS-stimulated IL-6: ↑ unstimulated IL-6 in physically active subjects; ↓ IL-6 production in RT with low dose LPS after program; ↑ unstimulated IL-6 in RT after program
McKenzie, 2017(118)	Community-dwelling older adults recovering from hip fracture (incurred in preceding 2-6 months), and recently (1-12 weeks) discharged from 8-12 weeks of usual-care physical therapy – n=7 (3 ♂, 4 ♀) – 78.4 (SD 13.3) years	Age-, sex-, and BMI-matched controls (tissue from a previous study) – n=8 (4 ♂, 4 ♀) – 76.4 (SD 4.8) years	- Training program: 3 sessions/week for 12 weeks - CG: no training program - Session: 60-80 min with high-intensity exercises and task orientation (protein drink provided after each session)	Vastus lateralis muscle biopsy – pre and post program	qPCR (IL-6, TLR2, TLR4 TAK1, HMGB1, MyD88, TRAF6, NF-κB)	TLR2, TLR4 = (no group differences, no impact exercise)	Gene expression pre-post: ↓ MyD88, TAK1, NF-κB, IL-6 after exercise training Gene expression in comparison with healthy controls: MyD88, TRAF6, TAK1 and HMGB1 were elevated compared to control before and after the program; IL-6 and NF-κB were elevated compared to control before the program, but normalised thereafter
Nader, 2010(126)	Autoimmune inflammatory myopathy (5 dermatomyositis patients and 3 polymyositis patients) – median 51 (range 44-61) years	/	- Training program: 3 sessions/week for 7 weeks - Upper and lower body exercise: 10 voluntary repetition maximum	Vastus lateralis muscle biopsy – 1 week pre and post program	Gene expression microarray qPCR (IRAK3, IL-10Rβ Immunohistochemistry (IL-1α, IL-1β, IL-1Ra, IL-1RI, IL-1RII, HMGB-1)	↓ TLR8	Microarray and qPCR: ↓ IRAK3, IL10-Rβ, HMGB-1 Immunohistochemistry: IL-1α, IL-1β, IL-1Ra, IL-1RI, IL-1RII =
Phillips, 2012(142)	Obese postmenopausal women without regular exercise in the previous 6 months – n=11 – 64.8 (SD 2.4) years	Obese postmenopausal women without regular exercise in the previous 6 months – n=12 – 66.4 (SD 2.8) years	- Exercise bout ≥1 week after the ending of an acclimatisation training, followed by a training program and repetition of the exercise bout ≥1 week after the program - Training program: acclimatisation week (3 sessions/1 week), followed by 3 sessions/weeks for 12 weeks - CG: acclimatisation at start and after 12-week intervention, intervention with control activities and resting control trial - Exercise bout: 3 sets of 10 exercises at 8RM - Upper and lower body exercise: 3 sets of 10 exercises at 8RM	Venous blood – pre, 4 min, 2 and 24h after exercise (or resting) trial Subcutaneous adipose tissue (SCAT) – 400 mg of the abdominal region at baseline and 48h after the last exercise session (or 1 week after 8RM assessment in CG)	Whole blood stimulation with LPS (24h) with ELISA qPCR (blood: TLR4, SCAT: TLR4)(only at pre time points)	TLR4 =	Cell count: ↑ total leukocytes in exercise group post and 2h after exercise with normalisation after 24h; ↑ total leukocytes in CG at 2h with normalisation after 24h Cell counts at baseline: ↓ monocyte number in exercise group after program Plasma cytokines: ↓ resting TNF-α in exercise group after program; ↑ IL-6 post and 2h after both exercise trials in exercise group with normalisation after 24h; ↑ IL-6 at 2h after both control interventions in CG with normalisation after 24h; ↓ mean IL-6 in CG after control intervention LPS-stimulated IL-10: mean ↑ in exercise group compared to CG; ↓ in CG after intervention LPS-stimulated TNF-α: mean ↑ at 2h in both groups, with further ↑ at 24h in exercise group and normalisation in CG
Prestes, 2015(144)	Sedentary non-obese elderly women: - resistance training with linear periodisation (RT/LP) – n=20 – 69.20 (SD 6.05) years - resistance training with undulating periodisation (RT/UP) – n=19 – 65.52 (SD 4.72) years	Sedentary non-obese elderly women – n=10 – 66.90 (SD 7.56) years	- Training program: 2 sessions/week for 16 weeks - CG: no training program - Upper and lower body exercise: 40-50 min - LP: build-up from 12-14 RM to 6-8 RM - UP: training loads varied on daily basis	Venous blood – pre and post program	ELISA (IL-1β, IL-1Ra, IL-10, IL15, irisin, TLR4)	TLR4 =	Cytokines: ↑ baseline irisin in LP compared to control and UP; no other group differences or impact of training

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Rodriguez-Miguelez, 2014(154)	Healthy elderly subjects – n=16 (mixed gender) – 69.1 (SEM 1.1) years	Healthy elderly subjects – n=10 (mixed gender) – 70.0 (SEM 0.9) years	- Training program: 2 sessions/week for 8 weeks - CG: normal daily routines - Upper and lower body exercise: 10 min warm-up, exercise at 60-80% 1RM	Venous blood – pre and post program	ELISA (CRP, TNF-α) Western blot (HSP60, HSP70, TLR2, TLR4, TRIF, IKKi/IKKε, MyD88, p65, IRF, pIRF3, IRF7, pIRF7, ERK1/2, pERK1/2, p38, pP38, TNF-α, IL-10) qPCR of PBMC (IL-10, TNF-α)	↓ TLR2,TLR4 after program (↔ CG =)	MyD88 and p65 protein: ↓ after program (↔ CG =) pP38 and pERK1/2 protein: ↓pP38 and ↑pERK1/2 after program (↔ CG =); total p38 and ERK1/2 = TRIF, IKK, pIRF3 and pIRF7 protein: ↓TRIF, IKK, pIRF3 and pIRF7 after program (↔ CG =) IL-10 and TNF-α mRNA and protein: ↑ IL-10 mRNA and protein after program (↔ CG =); TNF-α mRNA or protein = Plasma CRP and IL-6: ↓ CRP and IL-6 after program (↔ CG =) HSP60 and HSP70: ↑HSP70 after program; ↓HSP60 after program (↔ CG =)

Age is given as mean unless otherwise stated. Abbreviations: 1RM, one-repetition maximum; CD, cluster of differentiation; CG, control group; CRP, c-reactive protein; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal-regulated protein kinase; HMGB, high mobility group box; HSP, heat shock protein; IFN, interferon; IKK, IκB kinases; IL, interleukine; IRAK, IL-1R-associated kinase; IRF, interferon regulatory transcription factor; LPS, lipopolysaccharide; MHR, maximal heart rate; min, minute; mRNA, messenger RNA; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa B; PBMC, peripheral blood mononuclear cells; qPCR, quantitative polymerase chain reaction; ra, receptor antagonist; RT; resistance training; SD, standard deviation; SE, standard error; SEM, standard error of the mean; SIRT, sirtuin; TAK, transforming growth factor beta-activated kinase; TNF, tumor necrosis factor; TLR, toll-like receptor; TRAF, TNFR-associated factor; TRIF, TIR-domain-containing adaptor protein-inducing interferon-β.

Supplementary Table 5 | Summary of the characteristics of the articles investigating the effects of aerobic exercise programs.

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Bartlett, 2017(10)	Healthy inactive individuals: - HIIT – n=14 (4 ♂, 10 ♀) – 42 (SD 12) years - MICT – n=13 (5 ♂, 8 ♀) – 45 (SD 10) years	/	- Training program: 3 sessions/week for 10 weeks, for MICT group 2 additional self-administered sessions/week - HIIT: 18-25 min at >90% HR_{max} during sprint intervals - MICT: 30-45 min at 70% HR_{max}	Blood – pre and post program	Phagotest of whole blood with flow cytometry Phagoburst of whole blood with flow cytometry Flow cytometry (CD14, CD16, TLR2, TLR4) Multiplex luminometry (IL-1β, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17, GMCSF, TNF-α)	Neutrophil TLR2 and TLR4: = TLR2 expression: $CD14^+/CD16^-$ and $CD14^+/CD16^{bright}$ cells =; ↓ $CD14^+/CD16^{int}$ cells TLR4 expression: $CD14^+/CD16^-$ and $CD14^+/CD16^{int}$ cells =; ↓ $CD14^+/CD16^{bright}$ cells	Phagocytosis and oxidative burst: ↑ neutrophil phagocytosis and oxidative burst in both groups; ↑ monocyte phagocytosis in both groups; monocyte oxidative =, but % of monocytes producing an oxidative burst ↑ in both groups Cell count: leukocytes, monocytes =; ↑$CD14^+/CD16^-$ and ↓$CD14^+/CD16^{int}$ in both groups; ↓$CD14^+/CD16^{bright}$ in HIIT Neutrophils CD16: =
Bartlett, 2018(11)	Physically inactive adults with rheumatoid arthritis – n=12 (1 ♂, 11 ♀) – 64 (SD 7) years	/	- Training program: 3 sessions/week for 10 weeks - High-intensity interval walking: 30 min with ten ≥60 second intervals at 80-90% $VO2_{reserve}$ separated by lower-intensity intervals at 50-60% $VO2_{reserve}$	Venous blood – pre and 16-24h after exercise	Flow cytometry (CD14, CD16, TLR2, TLR4,HLA-DR, phagocytosis by whole blood) Insall chamber (neutrophil migration) Luminol-amplified chemiluminescence (neutrophil ROS) Sandwich immunoassay (IL-1β, IL-6, IL-10, TNF-α) Enzymatic colorimetric assay (NEFA)	Neutrophil TLR4: = Monocyte TLR2 and TLR4: ↓TLR2, TLR4 on intermediate monocytes after exercise; = on classical and non-classical monocytes	Cell count: no difference in total leukocytes or subpopulations Plasma cytokines and NEFA: no impact of exercise training Neutrophil function: ↑chemotactic index; ↑ chemotaxis; chemokinesis =; ↑ phagocytosis; ↑ ROS production after exercise training Neutrophil CD16: = Monocyte subpopulation: ↓$CD16^+$ monocytes, intermediate monocytes and non-classical monocytes after training Monocyte HLA-DR: ↓ on intermediate monocytes after exercise; = on classical and non-classical monocytes Monocyte function: ↑ phagocytosis after training

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Boehler, 2019(16)	Myositis patients – n=3	/	- Training program: 3 sessions/week for 12 weeks - Cycling: 1h at 70% VO_2max	Muscle biopsy – pre and post program	qPCR (TLR7)	↓ TLR7	/
Capó, 2014(22)	See "Capó *et al.* 2014" in Supplementary Table 3						
Child, 2013(35)	Overweight (BMI >25 kg/m²) sedentary (≤2 exercise sessions per week) men – n=11 – 24 (SD 5) years	/	- Training program: 3 sessions per week for 2 weeks - Cycling: ten 4-min intervals at 85% VO_2peak separated by 2-min rest periods	Venous blood – pre and post program	Flow cytometry (CD14, CD16, TLR2, TLR4)	TLR2 =; ↑ TLR4 on $CD14^+$ cells, $CD14^{++}/CD16^-$ and $CD14^+/CD16^{++}$ cells; TLR4 = on $CD14^{++}/CD16^+$ cells	Cell count: total leukocyte count, leukocyte and monocyte subpopulations =
Colleluori, 2019(40)	See "Colleluori *et al.* 2019" in Supplementary Table 4						
Estébanez, 2020(46)	Healthy elderly subjects without participation in aerobic exercise training in the last year – n=9 (2 ♂, 7 ♀) – 68.68 (SD 1.24) years	Healthy elderly subjects without participation in aerobic exercise training in the last year – n=5 (2 ♂, 3 ♀) – 70.78 (SD 1.51) years	- Training program: 2 sessions/week for 8 weeks - CG: maintained regular physical activity - Cycling: 5 min warm-up, 15-20 min at 70-75% MHR with progressive introduction of short periods of high intensity (1 min at 90-95%	Venous blood – pre and post program	Spectrophotometer (Reduced glutathione (GSH), total antioxidant capacity (TEAC)) Dichloro-dihydro-fluorescein diacetate assay (reactive oxygen species/reactive nitrogen species (ROS/RNS)) Western blot of PBMC (TLR4, 4-hydroxynonenal (4-	TLR4 = (no baseline difference, no impact of exercise)	GSH, TEAC and ROS/RNS: no baseline differences, no impact of exercise PC, 4-HNE and 3NT: no baseline difference, no impact of exercise
			MHR), 5 min active recovery		HNE), 3-nitrotyrosine (3NT)) OxyBlot kit (protein carbonyls (PC))		
Ferrari, 2019(53)	Patients with essential hypertension (immediately after diagnosis or in the context of sub-optimal treatment): - prehypertensive – n=14 (9 ♂, 5 ♀) – majority age group 61-70 years - hypertensive – n=30 (24 ♂, 6 ♀) – majority age group 41-60 years	Healthy normotensive subjects – n=24 (17 ♂, 7 ♀) – majority age group 41-60 years	- Training program: ≥4 sessions/week for 12 weeks (patient & control group) - Session: cycling or jogging with ≥30 min reaching heart rate corresponding to anaerobic threshold	Venous blood – pre and post program	PCR pyrosequencing (DNA methylation assay)	TLR2 = (non-significant increase in methylation after exercise)	PCR: TNF = (moderate non-significant increase in methylation)
Ghosh, 2015(65)	Healthy, non-smoking community-dwelling sedentary (≤1 exercise session/week) elderly – n=12 (8 ♂, 4 ♀) – 73.8 (2.1) years (11/12 participated to the exercise program)	Healthy, non-smoking community-dwelling sedentary (≤1 exercise session/week) young participants – n=13 (6 ♂, 7 ♀) – 25.5 (1.0) years	- Training program: 3-4 sessions/week for 16 weeks - CG: continuation habitual behaviour - Cycling: 20-45 min at 65-80% VO_2max (gradual increase in duration and intensity)	Vastus lateralis muscle biopsy – pre and 48-72h after program	ELISA (IL-6, TNF-α, LPS-binding protein) Limulus Amoebocyte Lysate assay (plasma LPS) Western blot (TLR4, NF-κB p50, NF-κB p65, JNK, pJNK, ERK, pERK, p38, pP38) qPCR (TLR4)	At baseline ↑ TLR4 (mRNA and protein) in elderly; no impact of exercise	Plasma cytokines: baseline IL-6 ↑ in elderly compared to young; no difference in TNF-α; no impact of exercise Plasma LPS and LPS-binding protein: baseline LPS and LPS-binding protein ↑ in elderly compared to young and not affected by exercise NF-κB p65 and NF-κB p50: baseline NF-κB p65 and NF-κB p50 ↑ in elderly compared to young; no impact of exercise JNK and pJNK: baseline pJNK/PNK ratio ↑ in elderly compared to young; no impact of exercise ERK, pERK, 38, pP38: no differences between groups or after exercise
Lackermair, 2017(92)	See "Lackermair *et al.* 2017" in Supplementary Table 3						
Mejías-Peña, 2016(119)	Healthy old subjects without experience in aerobic exercise training – n=16 (mixed gender) – 69.6 (SEM 1.0) years	Healthy old subjects without experience in aerobic exercise training – n=13 (mixed gender) – 70.0 (SEM 0.9) years	- Training program: 2 sessions/week for 8 weeks - CG: no intervention - Cycling: 25-30 min at 70-75% MHR (with progressive introduction of short periods of intense activity (90-95% MHR)	Venous blood – 5-6 days pre and post program	Western blot of PBMC (TLR2, TLR4, TRIF, MyD88)	TLR2, TLR4 = (between and within groups)	TRIF and MyD88 protein: no group differences or impact of training

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Nickel, 2011(130)	Male marathon runners: - obese non-elite (ONE) – n=15 – 40 (SDM 6) years - lean non-elite (LNE) – n=16 – 40 (SDM 6) years - elite (LE) – n=16 – (n=16)(40 (SDM 7) years)	/	- Training program: 4 sessions/week for 10 weeks - Running: continuous aerobic exercise and interval training with gradual increase in duration and intensity (average training mileage 35 km/week for ONE, 38 km/week for LNE and 54 km/week for LE)	Venous blood – pre and post program	Flow cytometry (leukocyte subpopulations) qPCR (TLR2, TLR4, TLR7, MyD88, NF-κB) Western blot (TLR2, TLR4, TLR7, MyD88)(8 subjects of LNE only) ELISA (IL-6 and TNF-α)	Baseline: TLR2, TLR4, TLR7 = Post-training TLR2 mRNA: ↑in LNE, similar patterns in other groups without significance Post-training TLR4 and TLR7 mRNA: ↑ in all groups Post-training western blot: TLR2 =; ↑ TLR4, TLR7	Leukocyte and monocyte count: = Dendritic cell subsets: ↓ myeloid DCs and ↑ plasmacytoid DCs in ONE at baseline with normalisation after program Baseline and post-training MyD88 and NF-κB: = Post-training western blot: MyD88 = IL-6: ↓ in LE at baseline with further decrease post program in LE TNF-α: ↓in LE at baseline; no changes after program
Niemiro, 2018(131)	Lean sedentary (≤30 min of moderate/high intensity exercise per week) individuals – n=17 (9 ♂, 8 ♀) – 23.9 (SD 5.4) years	Obese sedentary (≤30 min of moderate/high intensity exercise per week) individuals – n=10 (3 ♂, 7 ♀) – 29.0 (SD 8) years	- Training program: 3 sessions/week for 6 weeks (active & control group) - Cycling or running: 30-60 min at 60-75% MHR	Venous blood – 3-4 days pre and post program	MethoCult (CFU assay) Flow cytometry	Concentration of hematopoietic stem cells expressing TLR4 ↓ after exercise; TLR4 content ↑ after exercise; proportion of hematopoietic stem cells expressing TLR4 =	Cell count: ↓ circulating progenitor cells, ↓ adipose derived mesenchymal stem cells, ↓ common lymphoid progenitor cells in lean participants after exercise (↔ = in obese); ↓ hematopoietic stem cells in both groups after exercise program CFU count: baseline CFU potential of granulocytes and granulocyte/monocyte ↑ in obese participants; total number of CFU and CFU in granulocyte/monocyte ↑ after exercise
Reyna, 2013(150)	Sedentary (≤1 exercise bout/week) obese subjects with stable body weight: - non-diabetic – n=8 – 40 (SE 3) years - T2DM – n=11 – 50 (SE 3) years	Sedentary (≤1 exercise bout/week) subjects with stable body weight: - lean – n=17 – 39 (SE 2) years	- Training program: daily training for 15 days (patient & control groups) - Cycling: 4 identical periods of 8 min at 70% VO_2peak, 2 min at 90% VO_2peak and 2 min complete rest	Venous blood – pre and post program	Western blot mononuclear cells (TLR2, TLR4, ERK, JNK) ELISA (NF-κB p65)	TLR2 =; TLR4 ↑ at baseline in T2DM (significant) and obese (non-significant) compared to lean; no effect of exercise	ERK and JNK: baseline ERK phosphorylation ↑ in T2DM with non-significant ↓ after exercise; no impact of group or training on JNK phosphorylation NF-κB p65 binding: no impact of group or exercise
Robinson, 2015(153)	Subjects with prediabetes, BMI >24kg/m² and inactive lifestyle (<2 30-min bouts of moderate-to-vigorous exercise/week): - HIIT – n=20 (3 ♂, 17 ♀) – 52 (SD 10) years - MICT – n=18 (4 ♂, 14 ♀) – 52 (SD 10) years	/	- Training program: 5 sessions/week for 2 weeks - HIIT: four to ten 1-min intervals at 85-90% Wpeak with 1-min recovery at 20% Wpeak - MICT: 20-50 min at 32.5% Wpeak	Venous blood – pre and post program	ELISA (TNF-α, IL-1β, IL-6, IL-10) Flow cytometry (CD14, TLR2, TLR4) Whole blood stimulation with LPS and PamCSK4 (24h) with ELISA	TLR2: ↓ on lymphocytes; no change on monocytes and neutrophils TLR4: ↓ on lymphocytes and $CD14^+$ monocytes in both groups; ↓ on $CD15^+$ neutrophils in MICT (↔ HIIT =)	Cell count: no effect of training on leukocyte subpopulation concentrations Plasma cytokines: ↓ IL-10 after MICT LPS- and PamCSK4-stimulated blood: no effect of training
Sloan, 2018(172)	Healthy young adults without regular exercise and with VO_2max <43 mL/kg/min for men and <37 mL/kg/min for women – n=60 (28 ♂, 32 ♀) – 31 (SD 6) years	Healthy young adults without regular exercise and with VO_2max <43 mL/kg/min for men and <37 mL/kg/min for women – n=59 (28 ♂, 31 ♀) – 31 (SD 6) years	- Training program: 2 week run-in stretching period followed by 4 sessions/week for 12 weeks and 4 weeks of sedentary deconditioning - CG: 2 week run-in stretching period followed by maintenance of sedentary lifestyle - Session: 10-15 min warm-up, 30-40 min aerobic activity at 55-75% MHR, 10-15 min cool-down	Venous blood – after run-in period (2 weeks), post program (14 weeks) and post deconditioning (18 weeks)	Whole blood stimulation with LPS (4h) with Human Cytokine Array Western blot (TLR4)	TLR4 = (no impact of group, exercise or deconditioning)	Whole blood stimulation: no group differences; ↑ inducible TNF-α, inducible IL-6 post program compared to baseline in the trained group; ↓ inducible TNF-α, inducible IL-6 post deconditioning compared to post program in exercise group

Age is given as mean unless otherwise stated. Abbreviations: 3NT, 3-nitrotyrosine; 4-HNE, 4-hydoxynonenal; CD, cluster of differentiation; CG, control group; CFU, colony-forming unit; DC, dendritic cell; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal-regulated protein kinase; GMCSF, granulocyte macrophage colony-stimulating factor; GSH, reduced glutathione; h, hour; HIIT, high-intensity interval training; HR, heart rate; HLA-DR, human leukocyte antigen – DR isotype; IL, interleukine; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MHR, maximal heart rate; MICT, moderate-intensity continuous training; min, minute; mRNA, messenger RNA; MyD88, myeloid differentiation primary response gene 88; NEFA, non-esterified fatty acid; NF-κB, nuclear factor kappa B; PBMC, peripheral blood mononuclear cells; PC, protein carbonyls; qPCR, quantitative polymerase chain reaction; RNS, reactive nitrogen species; ROS, reactive oxygen species; SD, standard deviation; SDM, standard-deviation of the mean; SE, standard error; SEM, standard error of the mean; T2DM, type 2 diabetes mellitus; TEAC, total antioxidant capacity; TNF, tumor necrosis factor; TLR, toll-like receptor; TRIF, TIR-domain-containing adaptor protein-inducing interferon-β; W, power output.

Supplementary Table 6 | Summary of the characteristics of the articles investigating the effects of combined exercise programs.

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Colleluori, 2019(40)	See "Colleluori *et al.* 2019" in Supplementary Table 4						
Lambert, 2008(94)	Obese sedentary elderly with evidence of frailty – n=8 (4 ♂, 4 ♀) – 68.5 (SE 1.4) years	Obese sedentary elderly with evidence of frailty – n=8 (4 ♂, 4 ♀) – 69.6 (SE 1.4) years	- Training program: 3 sessions/week for 12 weeks - CG: energy-deficit diet and behaviour therapy - Session: 90 min with endurance exercise at 75-90% MHR and resistance exercise at 65-80% 1RM	Vastus lateralis muscle biopsy – pre and post program	qPCR (TLR4, IL-6, TNF-α) ELISA (serum IL-6 and TNF-α)	↓ TLR4 in exercise group; no difference in weight loss group	IL-6 and TNF-α mRNA: ↓ in exercise group; no change in weight loss group Serum IL-6 and TNF-α: =
Liu, 2015(108)	Non-insulin dependent T2DM without frequent exercise (<2/week for <15 min) – n=42 (12 ♂, 30 ♀) – 52.59 (SD 11.43) years: - conventional therapy (CT) – n=20 - intensive therapy (IT) – n=22	Healthy people – n=20 (7 ♂, 13 ♀) – 51.20 (SD 11.34) years	- Training program: home-based and supervised exercises: 3 aerobic sessions/week and 2-3 resistance sessions/week for 12 weeks - CT: regular drug treatment and diet guidance - IT: regular drug treatment, diet guidance and training program - CG: no intervention - Aerobic session: 40-60 min at 40-60% VO_2max	Venous blood – pre and post program (CG 1 measurement not related to the program)	qPCR of PBMC (TLR4, NF-κB p65) Western blot of PBMC (TLR4, NF-κB p65) ELISA (IL-18, IL-33)	TLR4 mRNA and protein: ↑ in T2DM at baseline compared to CG; after program mRNA ↓to control level in CT but still higher than IT with greater reduction; after program protein = in CT but ↓ to control level in IT	NF-κB p65 mRNA and protein: ↑ in T2DM at baseline compared to control; after program mRNA ↓to control level in CT but still higher than IT with greater reduction; after program protein = in CT but ↓ to control level in IT IL-18: ↑ in T2DM at baseline; after program = in CT but ↓ to control level in IT IL-33: ↓ in T2DM at baseline; after program ↑ in T2DM (more in IT), but still reduced compared to CG
			- Resistance session: 50-60% 1RM				
Munters, 2016(124)	Patients with definite or probable polymyositis or dermatomyositis, exercising ≤ 1/week – n=4 (1 ♂, 3 ♀) – median 66 (IQR 19) years	Patients with definite or probable polymyositis or dermatomyositis, exercising ≤ 1/week – n=4 (1 ♂, 3 ♀) – median 63 (IQR 16) years	- Training program: 3 sessions/week for 12 weeks - CG: maintained stable level of physical activity - Session: 60 min with 30 min cycling at 70% VO_2max and 30 min knee extensor exercises at 30-40% 1RM	Vastus lateralis muscle biopsy – pre and post program	Gene microarray (n=8)	↑ TLR7 after program	Gene microarray: ↑ HSPD1 gene (HSP60) after program in trained group; ↓ HSPA2 (HSP70-2) after program in trained group; ↑ IL28A in CG after program
Shimizu, 2011(168)	Healthy sedentary, independently living elderly – n=12 (3 ♂, 9 ♀) – 67.1 (SE 1) years	Healthy sedentary, independently living elderly – n=12 (4 ♂, 8 ♀) – 67.5 (SE 0.7) years	- Training program: 2 sessions/week with additionally a limited number of body weight resistance exercises for home (≥3 days/week) for 12 weeks - CG: no exercise Session: 10 min stretching, 10 min cycling, resistance training at 20-40% 1RM, 10 min stretching	Venous blood – pre and post program	Flow cytometry (CD14, TLR4, CD80)	$CD14^+/TLR4^+$ cells =	Leukocyte count: no influence of training on leukocyte, lymphocyte and monocyte number CD28: number of $CD28^+/CD8^+$ cells ↑ after training in the exercise group CD80: number of $CD14^+/CD80^+$ cells↑ after training in the exercise group
Soltani, 2020(174)	Female overweight or obese bachelor students with a sedentary lifestyle (≥6 months no participation in any exercise training) – n=13 – 21.3 (SD 1.37) years	Female overweight or obese bachelor students with a sedentary lifestyle (≥6 months no participation in any exercise training) – n= 13 – 20.69 (SD 1.54) years	- Training program: 5 sessions/week for 2 weeks - CG: no exercise intervention - Session: warm-up 10-12 min, upper and lower body cycling at 50-90% MHR and resistance	Venous blood – 5 days pre and 48h post program	qPCR of PBMC (TLR4, IRF3, NF-κB)	↓ TLR4 after exercise (↔ = in control group)	IRF3, NF-κB: = (no group differences or alterations by exercise)
			training at 40-60% 1RM for 25 min, cool-down 8-10 min				

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Stewart, 2005(180)	Subjects with (very) low physical activity score and estimated VO_2max < average: - young – n=14 – 24.9 (SE 4.7) years - older – n=17 – 71.0 (SE 4.3) years	Subjects (very) high physical activity score and estimated VO_2max good to excellent: - young – n=15 – 25.2 (SE 5.0) years - older – n=14 – 71.2 (SE 4.4) years	- Training program: 3 sessions/week for 12 weeks - CG: maintained usual levels of physical activity - Session: warm-up, 20 min endurance training, resistance training, stretching, cool-down	Venous blood – pre and post program	Flow cytometry (CD14, TLR2, TLR4) Whole blood stimulation with LPS or PGN (24h) with ELISA	TLR2 on $CD14^+$ cells: no training-effect; overall post-value ↓ compared to pre-value TLR4 on $CD14^+$ cells: ↓ in trained group; CG =	CD14: no significant differences LPS-stimulated IL-6: ↓ in trained groups; values post program lower in young compared to elderly LPS-stimulated IL-1β and TNF-α: no training effect; IL-1β values post program lower in young compared to elderly PGN-stimulated IL-6: no training effect; post program values lower in young compared to pre; pre values in young higher compared to elderly PGN-stimulated TNF-α: no significant differences PGN-stimulated IL-1β: post values on average lower than pre
Timmerman, 2008(187)	Physically inactive subjects (PI) (no regular physical activity in the last 6 months and VO_2max <26 mL/kg/min for male and <23 mL/kg/min for female) – n=15 (4 ♂, 11 ♀) – 71 (SD 5.74) years	Physically active subjects (PA) (exercising ≥3 days/week in the last 6 months and VO_2max >35 mL/kg/min for male and >28 mL/kg/min for female) – n=15 (8 ♂, 7 ♀) – 70 (SD 4.56) years	- Training program: 3 sessions/week for 12 weeks - CG: maintain physically active lifestyle - Session: treadmill running for 20 min at 60-70% HRR and resistance exercise for 30 min at 70-80% 1RM (2 sets of 8 exercises)	Venous blood – pre and post program	Flow cytometry (CD14, CD16, TLR4) Whole blood stimulation with LPS or LPS + polymyxin B (24h) with ELISA	TLR4: ↑ on classical monocytes from PI than from PA; no baseline difference $CD14^+$TLR4; no post-training differences	BMI: lower in PA at baseline Monocyte counts: ↓ inflammatory monocytes in PA at baseline; after training ↓ in PI Unstimulated whole blood: baseline TNF-α/$CD14^+$ monocyte lower in PA compared to PI; ↓ in PI after training LPS-stimulated whole blood: ↓TNF-α in PI after training; addition of polymyxine B blunted cytokine production

Age is given as mean unless otherwise stated. Abbreviations: 1RM, one-repetition maximum; CD, cluster of differentiation; CG, control group; ELISA, enzyme-linked immunosorbent assay; HHR, heart rate reserve; HSP, heat shock protein; IL, interleukine; IQR, interquartile range; IRF, interferon regulatory transcription factor; LPS, lipopolysaccharide; MHR, maximal heart rate; min, minute; mRNA, messenger RNA; NF-κB, nuclear factor kappa B; PBMC, peripheral blood mononuclear cells; PGN, peptidoglycan; qPCR, quantitative polymerase chain reaction; SD, standard deviation; SE, standard error; T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor; TLR, toll-like receptor.

Supplementary Table 7 | Summary of the characteristics of the articles investigating the effects of exercise programs which are not otherwise classifiable.

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
Ferrer, 2018(54)	Healthy elderly volunteers (n=116) with later categorisation into active and passive based on terciles of average MET in the last year: - active (1st tercile): male 62.5 (SEM 0.9) years, female 67.4 (SEM 1.0) years - sedentary (3rd tercile): male 64.6 (SEM 1.1) years, female 67.3 (SEM 1.1) years	/	/	Venous blood – after overnight fast	ELISA (IL-6) Guaiacol oxidation (MPO) qPCR of PBMC (TLR4, NF-κB, IL-1β, IL-1Ra, IL-6, IL-10, TNF-α) Western blot of PBMC (TLR2, TLR4)	TLR4 mRNA: ↑ in active males compared to active females TLR2 and TLR4 protein: ↑ TLR2 in active compared to the sedentary; TLR4 = (no impact of sex or activity)	Cell count: ↓ total leukocyte, neutrophil and lymphocyte counts in the active group Plasma IL-6 and MPO: ↓ levels of IL-6 in the active group; MPO = Gene expression: ↑ IL-10 in active males compared to sedentary males; ↑ NF-κB in active participants compared to sedentary; no impact of group or sex on IL-1Ra, IL-1β, IL-6, NF-κB or TNF-α
Flynn, 2003(58)	See "Flynn *et al.* 2003" in Supplementary Table 2						
Lundeland, 2012(110)	Healthy and well-trained male cadets – n=8 – 24.1 (2.5) years	/	- Ranger training course - Semi-continuous physical strain with restriction on sleep and food intake during 7 days	Venous blood – day 0, 3, 5 and 7	Flow cytometry (CD14, TLR4) Whole blood stimulation with saline or LPS (during 6h) with ELISA Gas chromatography (NEFAs)	Monocyte TLR4: = (non-significant ↑ expression over time)	Cell count: total leukocyte count ↑ until day 5 (with a parallel ↑ in granulocytes); monocyte count ↓ until day 3 followed by an increase Cytokine after LPS stimulation: TNF-α, IL-1β and IL-6 (per monocyte) ↑ at day 3 followed by ↓ to below baseline at day 5 and 7 Whole blood stimulation: ↑ TLR expression day 3-7 with saline- and LPS-stimulation
							Gas chromatography: NEFA ↑ on day 3, 5 and 7; ↑ UFA/SFA ratio

First author, year	Study population – n (sex distribution) – age	Control group if applicable – n (sex distribution) - age	Experimental design Exercise intervention	Study specimen – moment of collection	Analytical technique (analyses)	Outcome related to TLR	Other outcomes
McFarlin, 2004(116)	See "McFarlin *et al.* 2004" in Supplementary Table 2						
McFarlin, 2006(115)	Subjects with an active lifestyle and VO_2max > average - young – n=21 – 24 (SD 4.8) years - elderly – n=23 – 72 (SD 5) years	Subjects with an inactive lifestyle and VO_2max < average - young – n=19 – 24 (SD 5.1) years - elderly – n=21 – 69 (SD 4) years	/	Venous blood – after 72h without prior exercise	Flow cytometry (TLR4, CD14) Whole blood stimulation with LPS (24h) with ELISA	↑ TLR4 in inactive compared to active	Leukocyte counts: no differences leukocyte or monocyte count $CD14^+$ count: no significant differences LPS-stimulated IL-6: inactive ↑ compared to active LPS-stimulated IL-1β: young active ↑ compared to old active; old-inactive ↑ compared than young active LPS-stimulated TNF-α: inactive ↑ compared to active
Rodriguez-Miguelez, 2015(155)	Seniors without experience in whole body vibration – n=16 – 71.04 (SEM 1.5) years	Seniors without experience in whole body vibration – n=12 – 70.0 (SEM 0.9) years	- Whole body vibration training program - CG: normal routine - 2 sessions/week for 8 weeks of static and dynamic exercises (training volume and vibration frequency gradually increased)	Venous blood – 5-6 days pre and post program	qPCR of PBMC (TNF-α, IL-10) Western blot of PBMC (HSP60, HSP70, TLR2, TLR4, TRIF, MyD88, TNF-α) ELISA (TNF-α)	↓TLR2, TLR4 in trained group only	TNF-α serum level, mRNA and protein: mRNA =; ↓ plasma and protein in trained group IL-10 mRNA and protein: ↑ mRNA and protein after program in trained group HSP60 and HSP70: ↑HSP60 and ↓HSP70 after program in trained group MyD88, TRIF and p65: ↓MyD88, TRIF and p65 after program in trained group
Shimizu, 2015(167)	Competitive collegiate male kendo athletes: - placebo-supplemented group – n=9 – 19.7 (SE 0.9) years *- coenzyme Q10-supplemented group – n=9 (not considered in this review)*	/	- Kendo training camp - morning (2.5h) and afternoon session (3h) each day during 6 days	Venous blood – 14 days before camp and day 1, 3, and 5 of the camp and 7 days after finishing	Flow cytometry (CD14, TLR4)	$CD14^+/TLR4^+$ cells: ↑ day 3, 5 and post-training compared to baseline	Cell count: ↑ total leukocytes on day 3 with normalisation post-training; monocytes =
Timmerman, 2016(186)	Healthy elderly volunteers – n=26 (9 ♂, 17 ♀) – 68 (SD 4) years	/	/ (self-reported physical activity questionnaire and cardiorespiratory fitness test)	Vastus lateralis muscle biopsy – no physical activity in preceding 48h	Western blot (TLR4, membrane-bound TNF-α, soluble TNF-α)	TLR4 expression: ↑ in women compared to men; negative correlation with self-reported physical activity in men (also after correction for body fat or BMI); positive correlation with self-reported physical activity in women (not significant after controlling for body fat or BMI)	Membrane-bound and soluble TNF-α: no correlation with self-reported physical activity
Zheng, 2015(212)	Students of the university badminton club with 3/week 2h of exercise – n=20 (10 ♂, 10 ♀) – 20.8 (SD 2.1) years	Healthy sedentary students (CG) – n=25 (12 ♂, 13 ♀) – 21.8 (2.1) years	None	Venous blood - after obtaining informed consent	ELISA (IL-6, TNF-α, IFN-γ) Flow cytometry (DC subsets) PBMC or DC stimulation assay with heat-inactivated *S. pyogenes*, hepatitis B core antigen (24h) qPCR of PBMC (TLR2, TLR4 TLR7, MyD88)	Unstimulated, hepatitis core antigen or *S. pyogenes* stimulated mRNA: ↑ TLR2, TLR7 and in exercise group vs. CG except for TLR7 *in S. pyogenes* =; TLR4 =	Plasma cytokines: IL-6, TNF-α, IFN-γ = DC subsets: no differences between both groups Unstimulated PBMC culture: ↑IL-6 and TNF-α in CG vs. exercise group; IFN-γ = PBMC stimulation with hepatitis core antigen or *S. pyogenes*: ↑ IL-6, TNF-α and IFN-γ in exercise group vs. CG DC stimulation with hepatitis core antigen or *S. pyogenes*: ↑ IL-12 and IFN-α in exercise group vs. CG Unstimulated, hepatitis core antigen or *S. pyogenes* stimulated MyD88 mRNA: ↑ MyD88 in exercise group vs. CG

Age is given as mean unless otherwise stated. Abbreviations: CD, cluster of differentiation; CG, control group; DC, dendritic cell; ELISA, enzyme-linked immunosorbent assay; h, hour; HSP, heat shock protein; IFN, interferon; IL, interleukine; LPS, lipopolysaccharide; MET, metabolic equivalent of task; MPO, myeloperoxidase; mRNA, messenger RNA; MyD88, myeloid differentiation primary response gene 88; NEFA, non-esterified fatty acid; NF-κB, nuclear factor kappa B; PBMC, peripheral blood mononuclear cells; qPCR, quantitative polymerase chain reaction; ra, receptor antagonist; SD, standard deviation; SE, standard error; SEM, standard error of the mean; SFA, saturated fatty acid; TNF, tumor necrosis factor; TLR, toll-like receptor; TRIF, TIR-domain-containing adaptor protein-inducing interferon-β; UFA, unsaturated fatty acid.

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