The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease

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Abstract | Regular exercise reduces the risk of chronic metabolic and cardiorespiratory diseases, in part because exercise exerts anti-inflammatory effects. However, these effects are also likely to be responsible for the suppressed immunity that makes elite athletes more susceptible to infections. The anti-inflammatory effects of regular exercise may be mediated via both a reduction in visceral fat mass (with a subsequent decreased release of adipokines) and the induction of an anti-inflammatory environment with each bout of exercise. In this Review, we focus on the known mechanisms by which exercise — both acute and chronic — exerts its anti-inflammatory effects, and we discuss the implications of these effects for the prevention and treatment of disease.

Type 2 diabetes mellitus
A disorder of glucose homeostasis that is characterized by inappropriately increased blood glucose levels and resistance of tissues to the action of insulin. Recent studies indicate that inflammation in adipose tissue, liver and muscle contributes to the insulin-resistant state that is characteristic of type 2 diabetes mellitus, and that the anti-diabetic actions of peroxisome proliferator-activated receptor-γ agonists result, in part, from their anti-inflammatory effects in these tissues.

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The prevalence of obesity continues to rise worldwide and is being accompanied by a proportional increase in the incidence of other medical conditions, such as type 2 diabetes mellitus (T2D). Such conditions are associated with derangements in the interplay between metabolic and immune processes (immunometabolism)[1]. Moreover, obesity is associated with cardiovascular disease (CVD), chronic obstructive pulmonary disease, colon cancer, breast cancer, dementia and depression. Inflammation appears to be aetiologically linked to the pathogenesis of all of these conditions[2–6], and the development of a chronic low-grade inflammatory state has been established as a predictor of risk for several of them[7]. This inflammatory state is indicated by elevated levels of circulating inflammation markers, such as interleukin-6 (IL-6), tumour necrosis factor (TNF) and C-reactive protein (CRP). Importantly, physical inactivity and sedentary behaviour also increase the risk of these conditions[5,8–11]. An inactive lifestyle leads to the accumulation of visceral fat, and this is accompanied by adipose tissue infiltration by pro-inflammatory immune cells, increased release of adipokines and the development of a low-grade systemic inflammatory state[4]. This low-grade systemic inflammation has, in turn, been associated with the development of insulin resistance, atherosclerosis, neurodegeneration and tumour growth[6–8] (FIG. 1). Exercise has anti-inflammatory effects, and therefore, in the long term, regular physical activity can protect against the development of chronic diseases[8–11] (TABLE 1). In addition, exercise can be used as a treatment to ameliorate the symptoms of many of these conditions, and thus the concept that 'exercise is medicine'[12] (BOX 1) is increasingly promoted in the hope that the general population can be persuaded to partake in more physical activity.

Obviously exercise increases energy expenditure and burns off some of the body fat that would otherwise accumulate in individuals who consume more dietary energy than they need. In this sense, exercise reduces the risk of developing obesity and excessive adiposity. Regular exercise also promotes cardiovascular health, as it improves the blood lipid profile by decreasing the concentration of plasma triglycerides and low-density lipoprotein (LDL) particles and increasing the concentration of protective high-density lipoprotein (HDL) cholesterol[13]. These beneficial alterations in plasma lipids are presumed to limit the development of atherosclerosis. However, the protective effect of a physically active lifestyle against chronic inflammation-associated diseases (TABLE 1) may additionally be ascribed to an anti-inflammatory effect of exercise[14–16]. This may be mediated not only via a reduction in visceral fat mass (with a subsequent decreased production and release of pro-inflammatory adipokines) but also by induction of an anti-inflammatory environment with each bout of exercise[15,16]. In this Review, we explain the possible mechanisms by which exercise exerts its anti-inflammatory

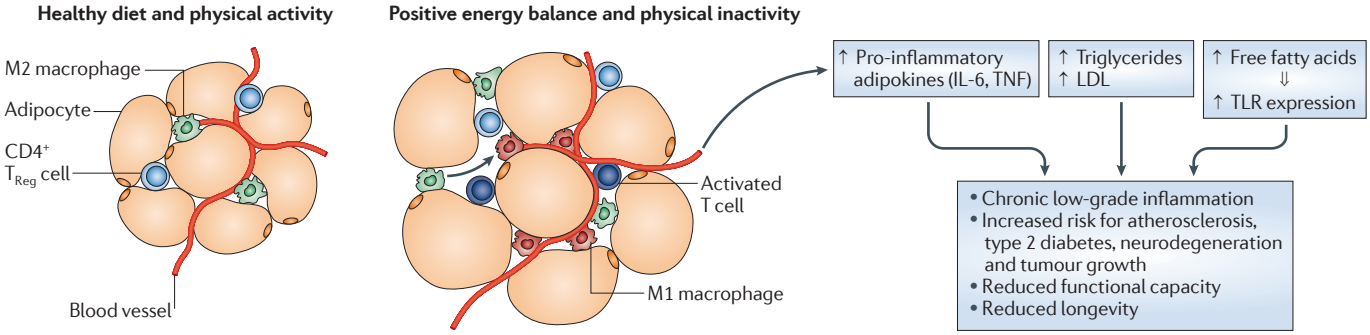

Figure 1 | **The effect of diet and physical activity on inflammation and disease.** A healthy diet and physical activity maintain the anti-inflammatory phenotype of adipose tissue, which is marked by small adipocyte size and the presence of anti-inflammatory immune cells, such as M2-type macrophages and CD4+ regulatory T (T_{Reg}) cells. A positive energy balance and physical inactivity lead to an accumulation of visceral fat and adipose tissue infiltration by pro-inflammatory macrophages and T cells. The pro-inflammatory M1 macrophage phenotype predominates and inflamed adipose tissue releases pro-inflammatory adipokines, such as tumour necrosis factor (TNF), which causes a state of persistent low-grade systemic inflammation. This may promote the development of insulin resistance, tumour growth, neurodegeneration and atherosclerosis. Atherosclerosis is exacerbated by the deleterious changes in the blood lipid profile that are associated with a lack of physical activity. LDL, low-density lipoprotein; IL-6, interleukin-6;TLR, Toll-like receptor.

Immunometabolism
This term has been recently introduced to describe the multilevel interactions between the metabolic and immune systems.

Adipokines
Factors, including cytokines, that are secreted from adipose tissue. Some adipokines promote inflammatory responses and metabolic dysfunction, whereas others have anti-inflammatory functions and beneficial effects on metabolic disorders.

Insulin resistance
A condition characterized by the inability of cells in the muscle, liver and adipose tissue to respond appropriately to endogenous insulin, resulting in increased blood glucose levels.

Triglycerides
The storage form of fat found in adipose tissue.

Low-density lipoprotein
(LDL). A protein–lipid complex in the blood plasma that facilitates the transport of triglycerides, cholesterol and phospholipids. High blood levels of LDL are associated with an increased risk of coronary heart disease.

High-density lipoprotein
(HDL). A protein–lipid complex in the blood plasma that facilitates the transport of triglycerides, cholesterol and phospholipids. High blood levels of HDL are associated with a decreased risk of coronary heart disease.

effect and briefly discuss the implications for the use of exercise as a medicine in the prevention and treatment of chronic disease. We also consider the impact of intensive training on infection risk for endurance athletes.

Anti-inflammatory effects of exercise

Recent reviews on the anti-inflammatory effects of exercise[15–17] have focused on three possible mechanisms: the reduction in visceral fat mass; increased production and release of anti-inflammatory cytokines from contracting skeletal muscle (such molecules are termed myokines[15,18]); and reduced expression of Toll-like receptors (TLRs) on monocytes and macrophages[17] (with subsequent inhibition of downstream responses, such as the production of pro-inflammatory cytokines and the expression of MHC and co-stimulatory molecules)[19]. In addition, mouse studies have revealed that the anti-inflammatory effects of exercise also rely on other mechanisms, such as the inhibition of monocyte and macrophage infiltration into adipose tissue[20] and the phenotypic switching of macrophages within adipose tissue[20]. Although these types of analysis are difficult to conduct in humans, analysis of human peripheral blood following exercise has revealed a reduction in the circulating numbers of pro-inflammatory monocytes[21] and an increase in the circulating numbers of regulatory T cells (T_{Reg} cells)[22,23]. This suggests that such mechanisms may also be involved in the anti-inflammatory effects of exercise in humans. However, there are some limitations in the study of the immunological effects of exercise (both acute and chronic) in humans; these types of study and their limitations are summarized in BOX 2.

Reduction in visceral fat mass. The accumulation of body fat — particularly in the abdomen, liver and muscles — is associated with increased all-cause mortality[24] and the development of T2D[25], CVD[26], dementia[27] and several cancers[28]. The expansion of the adipose tissue results in increased production of pro-inflammatory adipokines, such as TNF, leptin, retinol-binding protein 4, lipocalin 2, IL-6, IL-18, CC-chemokine ligand 2 (CCL2; also known as MCP1), CXC-chemokine ligand 5 and angiopoietin-like protein 2 (REF. 4). Conversely, the amounts of anti-inflammatory cytokines (for example, adiponectin and secreted frizzled-related protein 5) are reduced[4]. This leads to the development of a persistent state of low-grade systemic inflammation[29].

Regular exercise can reduce waist circumference and cause considerable reductions in abdominal and visceral fat, even in the absence of any loss of body weight, in both men and women regardless of age[30]. Furthermore, regular exercise results in higher circulating levels of adiponectin and lower levels of several circulating pro-inflammatory adipokines, including IL-6, TNF, retinol-binding protein 4 and leptin[31–33]. It is not known whether the levels of the other adipokines (mentioned above) are reduced in the blood following exercise, and further research is needed to address this. So, increased physical activity can bring about a reduction in systemic inflammation[29] via a decrease in pro-inflammatory adipokine secretion, which is a direct result of lowering the amount of fat stored in abdominal depots.

Release of IL-6 from contracting muscle. At rest, approximately 30% of circulating IL-6 arises from the adipose tissue[34], but only about 10% of this can be attributed to the adipocytes[35] with the remainder coming mostly from adipose tissue-resident macrophages. Other sources of circulating IL-6 include blood leukocytes (predominantly monocytes), the brain and the liver. During and following exercise of sufficient load, the active skeletal muscle markedly increases both cellular and circulating levels of IL-6 (REF. 36). With prolonged exercise (over 2.5 hours), IL-6 levels can increase over 100-fold, although more modest increases are reported with exercise of a shorter duration[37]. Increases have also been

Table 1 | **A summary of the associations between physical activity and major diseases***

Disease	Evidence that physical activity may lower disease risk and/or have therapeutic value in treating disease
CHD	A large body of epidemiological evidence demonstrates that high levels of physical activity and physical fitness are associated with a lower risk of developing CHD. RCTs show that regular physical activity can favourably modify CHD risk factors, including (but not limited to) dyslipidaemia, hypertension and obesity. RCTs also show that physical activity improves survival in CHD patients.
Stroke	Evidence suggests that high levels of physical activity and physical fitness reduce the risk of stroke, although the data are not as compelling as those for CHD. RCTs show that physical activity can lower (but not necessarily normalize) blood pressure in hypertensive individuals.
Cancer	High levels of physical activity are associated with a lower risk of colon and breast cancer. Physical activity may lower cancer risk by systemic mechanisms (such as reduced body fat and insulin levels, and enhanced immune function) and site-specific mechanisms (namely, reduced levels of sex steroid hormones for breast cancer, and decreased bowel transit time for colon cancer). Some observational and RCT evidence supports a therapeutic role for physical activity in preserving mobility and function in cancer patients.
T2D	Observational epidemiological evidence consistently demonstrates an association between high levels of physical activity and/or fitness and a reduced risk of developing T2D. RCTs show that lifestyle intervention (diet and physical activity) can lower body mass, improve glucose tolerance and reduce the risk of developing T2D in high-risk patients. In patients with T2D, high levels of physical activity and physical fitness are associated with a reduced risk of CHD and all-cause mortality.
Dementia	Observational epidemiological studies indicate that higher levels of physical activity are associated with a lower risk of cognitive decline and dementia in older adults. Some limited evidence is available from RCTs to suggest that physical activity induces modest improvements in cognition in individuals who are at increased risk of Alzheimer's disease or other forms of dementia.
Other	There is some evidence from observational and intervention studies to support a role for physical activity in enhancing physical function and improving quality of life in those suffering from chronic heart failure, chronic obstructive pulmonary disease, depression, intermittent claudication, osteoarthritis and osteoporosis.

CHD, coronary heart disease; RCT, randomized controlled trial; T2D, type 2 diabetes mellitus. *See REFS 8,9 for further detail.

Regulatory T cells
(T_{Reg} cells). A specialized subpopulation of T cells that acts to suppress activation of the immune system and thereby maintains immune system homeostasis and tolerance to self antigens. These cells are involved in shutting down immune responses after they have successfully tackled invading microorganisms, and also in regulating immune responses that may potentially attack one's own tissues (autoimmunity).

Leptin
A regulatory hormone that is produced by adipocytes. When released into the circulation, it influences the hypothalamus to control appetite, and its production correlates with the amount of adipose tissue.

Adiponectin
A cytokine released from adipocytes that has anti-inflammatory effects and acts as an insulin sensitizer.

Cortisol
A steroid hormone secreted from the adrenal cortex in response to stress that has anti-inflammatory as well as catabolic effects.

Adrenaline
A catecholamine secreted from the adrenal medulla in response to stress that has effects on the cardiovascular system (for example, increased heart rate and peripheral vasoconstriction) and on metabolism (for example, increased glycogen breakdown and lipolysis). It also has some immunosuppressive effects (for example, decreased pro-inflammatory cytokine production by monocytes and lymphocytes).

noted using intermittent exercise protocols of relatively short duration[38]. The increase in IL-6 during exercise is transient, normally returning to resting levels within 1 hour after exercise. The plasma IL-6 concentration increases exponentially with exercise duration, and a major stimulus of its synthesis and release appears to be a fall in muscle glycogen content[39,40]. Increases in intracellular calcium levels and increased formation of reactive oxygen species are also capable of activating transcription factors that are known to regulate IL-6 synthesis[37].

The transient rise in circulating IL-6 during exercise appears to be responsible for a subsequent rise in circulating levels of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1RA), and it also stimulates the release of cortisol from the adrenal glands[41]. This is demonstrated with the observation that intravenous infusion of IL-6 mimics the acute anti-inflammatory effects of a bout of exercise, both with regard to elevation of plasma IL-10, IL-1RA and cortisol[41] and with regard to suppression of endotoxin-stimulated increases in TNF levels[42].

IL-1RA is secreted mainly by monocytes and macrophages and inhibits the pro-inflammatory actions of IL-1β[43]. IL-10 is known to be produced primarily by T_{Reg} cells but also by T helper 2 (T_H2) cells, T_H1 cells, T_H17 cells, monocytes, macrophages, dendritic cells (DCs), B cells and $CD8^+$ T cells[44]. Irrespective of the cellular source, the principal function of IL-10 appears to be the downregulation of adaptive immune responses[45] and minimization of inflammation-induced tissue damage. In detail, IL-10 downregulates the expression of MHC molecules, intercellular adhesion molecule 1 (ICAM1) and the co-stimulatory molecules CD80 and CD86 on antigen-presenting cells, and it has also been shown to promote the differentiation of DCs expressing low levels of MHC class II, CD80 and CD86 (REF. 44). In addition, IL-10 downregulates or completely inhibits the expression of several pro-inflammatory cytokines and other soluble mediators, thereby further compromising the capacity of effector T cells to sustain inflammatory responses[44,45].Thus, IL-10 is a potent promoter of an anti-inflammatory state.

Circulating levels of IL-10 are lower in obese subjects, and acute treatment with IL-10 prevents lipid-induced insulin resistance[46]. Moreover, IL-10 increases insulin sensitivity and protects skeletal muscle from obesity-associated macrophage infiltration, increases in inflammatory cytokines and the deleterious effects of these cytokines on insulin signalling and glucose metabolism[46].

The action of IL-6 and the subsequent cascade of anti-inflammatory cytokines is not the only mechanism responsible for the health benefits that are associated with exercise, as elevations of IL-6 do not occur with short durations of low to moderate intensity exercise[37] despite the known health benefits (for example, reduced risk of heart disease) associated with only very moderate increases in physical activity above that of a sedentary lifestyle[47,48].

Increased levels of circulating cortisol and adrenaline. Secretion of the adrenal hormones cortisol and adrenaline is increased during exercise owing to activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system (SNS). Impulses from the motor centres

Box 1 | **Exercise is medicine**

Exercise is now considered to be not only of prophylactic value, but also an effective therapy for many conditions and diseases. Perhaps the strongest evidence for the role of exercise in disease prevention comes from randomized controlled trials that evaluated the effectiveness of lifestyle intervention in preventing type 2 diabetes mellitus (T2D)[103]. These studies have demonstrated conclusively that lifestyle intervention (combined diet and exercise) is effective in preventing T2D in groups of individuals who are at high risk of the disease. A limitation of these studies is that the independent effects of exercise and diet in preventing T2D were not isolated. However, the effectiveness of exercise alone is supported by the findings of the Finnish Diabetes Prevention Study[104]. Among those in the intervention group of this study who did not reach the goal of losing 5% of their initial body mass, but who achieved the goal of exercising for more than 4 hours per week, the odds ratio of developing T2D was 80% lower than in intervention participants who remained sedentary.

In addition, exercise appears to have major benefits for the treatment of T2D[105], and prospective observational studies indicate that high levels of physical activity and/or physical fitness are effective in reducing the risk of cardiovascular disease (CVD) and all-cause mortality in T2D patients[106,107]. Inflammation has been implicated in the pathogenesis of T2D[108], and it is therefore likely that the therapeutic benefits of exercise for those with T2D are due, at least in part, to the well-established anti-inflammatory effects of regular exercise[14–16].

There is also good evidence that exercise is effective in preventing several other major diseases, particularly CVD[109], breast cancer[102,110] and colon cancer[102,111], and some evidence supports a role for exercise in preventing dementia[112]. Other studies have suggested that exercise could be used as a therapy for chronic obstructive pulmonary disease, chronic kidney disease, asthma and osteoporosis[8,9].

Hypothalamic–pituitary–adrenal axis
A major component of the stress system that consists of the paraventricular nucleus (PVN) of the hypothalamus, the anterior pituitary gland and the adrenal cortices. Corticotropin-releasing hormone and vasopressin secreted by PVN neurons into the hypophyseal portal system stimulate pituitary cells to produce and secrete adrenocorticotropic hormone (ACTH) into the general circulation. ACTH then stimulates cortisol secretion by the adrenal glands.

Sympathetic nervous system
A part of the nervous system that serves to accelerate the heart rate, constrict blood vessels, raise blood pressure and mobilize metabolic fuels. It is responsible for the 'fight-or-flight response' to stress and physical activity (that is, the non-volitional preparation of the organism for emergency situations).

Adrenocorticotropic hormone
A peptide hormone secreted from the anterior pituitary gland that stimulates the release of cortisol from the adrenal glands.

in the brain as well as afferent impulses from working muscles elicit an intensity-dependent increase in sympathoadrenal activity. These neural signals also induce the release of some hypothalamic releasing factors, which increase the secretion of certain pituitary hormones, including adrenocorticotropic hormone (ACTH)[49]. Increased SNS activity stimulates the release of the catecholamines adrenaline and noradrenaline from the adrenal medulla within seconds of the onset of exercise, and ACTH stimulates cortisol secretion from the adrenal cortex within minutes. These hormonal responses usually precede the rise in circulating concentrations of cytokines, and the magnitude of the elevations in plasma cortisol and adrenaline levels is related to the intensity and duration of exercise[49]. Cortisol is known to have potent anti-inflammatory effects[50], and catecholamines downregulate the lipopolysaccharide (LPS)-induced production of cytokines (including TNF and IL-1β) by immune cells[51]. Cortisol secretion is also augmented by the aforementioned rise in circulating IL-6 from working skeletal muscle[41]. Thus, hormones, myokines and cytokines all contribute to the anti-inflammatory effect of exercise (FIG. 2).

Inhibition of macrophage infiltration into adipose tissue. Macrophages and T cells that infiltrate adipose tissue in obesity are known to regulate the adipose tissue's inflammatory state[52,53]. Thus, the migration of peripheral blood mononuclear cells (PBMCs) towards sites of inflammation, including adipose tissue and damaged vascular endothelium, is central to the development of sustained tissue inflammation[54–57]. It has been suggested that the increased size of the adipocytes, rather than an overall increase in adipose tissue mass, triggers macrophage infiltration[58], and it has been speculated that the recruitment of macrophages may be stimulated by the chemokines CCL2 and CCL3 (also known as MIP1α)[55,59].

Exercise may limit the movement of PBMCs into inflamed adipose tissue, although there is little evidence to support this at present[20]. The migration of PBMCs from the circulation into the tissues is a tightly regulated process. It requires a gradient of chemokines that are released from the inflamed tissue (including from immune cells residing within the tissue), the expression of complimentary chemokine receptors on PBMCs and the expression of adhesion molecules on both immune and endothelial cells. Acute bouts of exercise reduce T cell migration towards the supernatants from human airway epithelial BEAS-2B cells infected with rhinovirus in a manner that is independent of any involvement of adhesion molecules or exercise-induced elevations of cortisol or catecholamines[60]. However, it is known that the stress induced by acute exercise results in the release of chemokines from multiple sources into the circulation[61], and sustained exposure of PBMCs to physiological concentrations of chemokines (including CCL2) results in chemokine receptor internalization[62]. This is thought to serve as a negative feedback mechanism to reduce migration and thereby terminate the accumulation of PBMCs in inflamed tissue. It is possible, therefore, that an active lifestyle causes repeated short-lasting elevations in plasma levels of chemokines, which act over time to downregulate expression of their receptors on PBMCs and restrict migration of these cells towards adipose tissue. However, this potential mechanism needs to be explored further in humans. Conversely, there is some evidence from murine studies in support of the concept that exercise inhibits the release of chemokines from adipose tissue and in this way reduces macrophage infiltration, although whether this occurs in humans is not clear[54,63].

In a mouse model, training was reported to decrease the tissue expression of ICAM1 (REF. 20), which has a role in the adhesion of inflammatory cells to vascular endothelium, the extracellular matrix and epithelium, and also mediates interactions between T cells and target cells. Signal transduction downstream of these interactions leads to T cell activation, proliferation, cytotoxicity and cytokine production. ICAM1 expression is known to be increased in obesity in humans[64], and blocking ICAM1 in obese mice prevented macrophage infiltration into adipose tissue[65]. Moreover, circulating ICAM1 levels were reduced in patients with T2D following 6 months of progressive aerobic exercise training, without changes in body mass or waist circumference[66]. Obviously, further studies in humans are required to ascertain the effect of exercise training on ICAM1 expression in adipose tissue, but ICAM1 might also have a role in the exercise-induced reduction of macrophage infiltration into adipose tissue.

Macrophage activation results in two separate polarization states: M1 and M2 (REF. 67). M1-type macrophages produce TNF, IL-6 and nitric oxide, whereas M2-type macrophages produce anti-inflammatory cytokines and arginase. Therefore, M1-type macrophages induce an inflammatory state and M2-type macrophages subdue

Box 2 | **Studying immune responses to exercise in humans**

The study of the immunological effects of exercise in humans is a growing area of research, and more than 1,400 original studies and 500 review articles have been published in the past 15 years. Studies either investigate the effects of exercise as a behavioural or lifestyle factor *per se*, or use exercise as a non-clinical human model of the body's response to physiological stresses, such as sepsis or trauma. There are two main types of exercise used in these investigations in humans: moderate (recreational) exercise or intensive periods of exercise of differing durations, which may be continuous or intermittent. Study designs include acute exercise (single bout) protocols, cross-sectional comparisons of different activity levels and longitudinal studies over a period of weeks or months.

The effects of exercise on immune measures have been assessed in numerous ways, primarily in purified cell populations or in whole blood. The parameters that are commonly investigated include: phenotypic alterations in circulating cells; expression of markers of activation or apoptosis; lymphocyte proliferation; cytokine and immunoglobulin production; natural killer cell cytotoxicity; neutrophil phagocytosis, degranulation and oxidative burst; and cell chemotaxis or migration. Assays to determine concentrations of soluble markers — such as immunoglobulins, cytokines, shed adhesion molecules and cytotoxic enzymes — are routinely used in this field. Levels of mucosal immune factors, particularly salivary IgA, have received much attention in the exercise immunology literature owing to their established negative association with subsequent respiratory infections in athletic populations[96,99,113].

The limitations of many studies in this field are that only peripheral blood measurements have been used in the majority of investigations into immunological responses to exercise in humans, and that *in vitro* measures have been used extensively to model the complex situation *in vivo*. However, delayed-type hypersensitivity responses and antibody titres following vaccination have been used in this regard to good effect in some human exercise studies.

inflammation in adipose tissue. Inflamed adipose tissue appears to be associated with a preferential recruitment of M1-type macrophages and/or a phenotypic switch of adipose tissue macrophages towards the M1 phenotype[68]. Therefore, it is possible that the attenuated inflammatory state of adipose tissue that is associated with chronic exercise training occurs by both suppression of macrophage infiltration and acceleration of phenotypic switching from M1- to M2-type macrophages. Indeed, a recent study in mice fed a high-fat diet to induce obesity provided some evidence that exercise training induces this phenotypic switching from M1- to M2-type macrophages in adipose tissue and inhibits M1-type macrophage infiltration into adipose tissue[20]. However, studies in humans are still scarce.

Downregulation of TLR expression. TLRs are highly conserved transmembrane proteins that have an important role in the detection of microbial pathogens and in the recognition of endogenous danger signals released following tissue damage, such as heat shock proteins[69]. Activation of TLR signalling results in increased expression and secretion of pro-inflammatory cytokines and thus has an important role in mediating systemic inflammation[70]. Evidence is now emerging that TLRs may be involved in the link between a sedentary lifestyle and inflammation and disease. Exercise training studies and cross-sectional comparisons between physically active and inactive subjects have shown that blood monocytes from physically active individuals have a reduced inflammatory response to endotoxin stimulation *in vitro*. These cells also have decreased TLR4 expression (at both cell surface protein and mRNA levels)[17,19], which is associated with decreased inflammatory cytokine production[71].

Following an acute, prolonged bout of strenuous exercise, the expression of TLR1, TLR2 and TLR4 on monocytes is decreased for at least several hours[19,72,73]. Prolonged exercise also results in a decreased induction of co-stimulatory molecules and cytokines following stimulation with known TLR ligands, such as LPS and zymosan[71]. Whether this reduction in cell surface expression of TLRs is due to downregulation of TLR gene expression, shedding of TLRs from the cell surface or re-internalization by the cell remains to be established. The precise physiological stimulus that mediates an exercise-induced decrease in cell surface TLR expression is not known; however, several possible signals have been implicated, including anti-inflammatory cytokines, stress hormones and heat shock proteins[19].

The evidence discussed above points to a downregulation of TLR expression and subsequent downstream inflammatory signalling cascades with acute exercise. However, as prolonged exercise increases lipolysis and elevates plasma levels of free fatty acids, which are ligands for TLR2 and TLR4 (REF. 74), it might be surmised that exercise could induce inflammatory cascades via activation of TLRs. However, there is no direct evidence for this, and LPS-stimulated cytokine production by blood monocytes is clearly reduced, not increased, following prolonged exercise[42,71,75].

Reduced numbers of pro-inflammatory monocytes in blood. There are two main populations of monocytes: classical ($CD14^{hi}CD16^{-}$) and non-classical ($CD14^{low}CD16^{+}$ or $CD14^{hi}CD16^{+}$). These subsets differentially express cell surface TLR4, with the inflammatory $CD14^{low}CD16^{+}$ monocytes expressing 2.5 times as much cell surface TLR4 as the other populations[76]. Despite constituting only 10% of the total monocyte population, inflammatory monocytes contribute significantly to the inflammatory potential of the monocyte pool as a whole[77]. The percentage of circulating inflammatory monocytes is elevated in patients with rheumatoid arthritis[78], CVD[79] and T2D[80], and it has been suggested that inflammatory monocytes play a significant role in the pathogenesis of several diseases linked to inflammation. Transient increases in the numbers of inflammatory monocytes have been observed after a single, acute bout of intense exercise[81], followed by a rapid return to

Noradrenaline
A catecholamine secreted from sympathetic nerve endings that has effects on the cardiovascular system (for example, increased heart rate and peripheral vasoconstriction) and on metabolism (for example, increased glycogen breakdown and lipolysis). It also has some immunosuppressive effects (for example, decreased pro-inflammatory cytokine production by monocytes and lymphocytes).

M1-type macrophages
Macrophages that are activated in the presence of T_H1-type cytokines, such as interferon-γ, and produce, among other molecules, inducible nitric oxide synthase and nitric oxide.

M2-type macrophages
Macrophages that are activated in the presence of T_H2-type cytokines, such as interleukin-4 (IL-4) or IL-13, and express arginase 1, the mannose receptor CD206 and the IL-4 receptor α-chain.

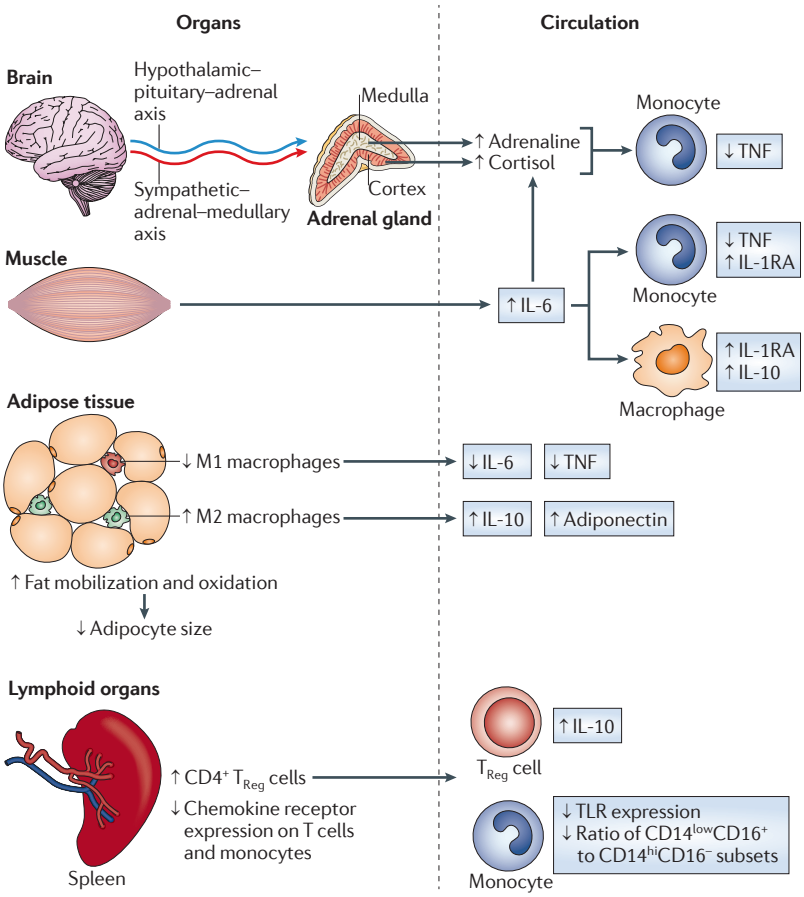

Figure 2 | **Potential mechanisms contributing to the anti-inflammatory effects of exercise.** Activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system (SNS) leads to the release of cortisol and adrenaline from the adrenal cortex and medulla, respectively. These hormones inhibit the release of tumour necrosis factor (TNF) by monocytes. Interleukin-6 (IL-6) produced by contracting skeletal muscle also downregulates the production of TNF by monocytes and may stimulate further cortisol release. Acute elevations in IL-6 stimulate the release of IL-1 receptor antagonist (IL-1RA) from monocytes and macrophages, thus increasing the circulating concentrations of this anti-inflammatory cytokine. Exercise training mobilizes regulatory T (T_{Reg}) cells (which are a major source of the anti-inflammatory cytokine IL-10) and decreases the ratio of inflammatory ($CD14^{low}CD16^{+}$) monocytes to classical ($CD14^{hi}CD16^{-}$) monocytes. Following exercise, $CD14^{hi}CD16^{-}$ monocytes express less Toll-like receptor 4 (TLR4), and thereby induce a reduced inflammatory response marked by lower levels of pro-inflammatory cytokines and reduced adipose tissue infiltration. Exercise also increases plasma concentrations of key inflammatory immune cell chemokines; repeated elevations of such chemokines may lead to a downregulation of their cellular receptors, resulting in reduced tissue infiltration. A reduction in adipose tissue mass and adipocyte size, along with reduced macrophage infiltration and a switch from an M1 to an M2 macrophage phenotype, may contribute to a reduction in the release of pro-inflammatory cytokines (such as IL-6 and TNF) and an increase in the release of anti-inflammatory cytokines (such as adiponectin and IL-10) from adipose tissue.

baseline numbers during recovery. However, regular exercise appears to reduce the proportion of inflammatory monocytes in the circulation in the resting state. For example, a cross-sectional comparison of healthy, physically inactive elderly men and women with an age-matched physically active group indicated that sedentary people have a twofold higher percentage of circulating inflammatory monocytes[21]. Furthermore, 12 weeks of regular exercise training markedly reduced the percentage of inflammatory monocytes in the inactive group to the level of the active group, and endotoxin-stimulated TNF production was reduced substantially after the training intervention. Based on previous reports that glucocorticoid therapy selectively depletes $CD14^{low}CD16^{+}$ monocytes[82], it is interesting to speculate that exercise-induced transient spikes in plasma cortisol levels may have a role in reducing the number of $CD14^{low}CD16^{+}$ monocytes.

Of course, a reduction in the number of inflammatory monocytes in the blood could also be indicative of increased monocyte infiltration into the tissues or migration of pro-inflammatory monocytes into the lymphoid organs[83]. However, this notion is not supported by murine studies that demonstrate reduced leukocyte infiltration and inflammation in dermal wound sites after exercise[84]. Further analysis and functional studies are needed in humans to confirm that exercise reduces the numbers of pro-inflammatory monocytes and that this contributes to its anti-inflammatory effects.

Increased circulating numbers of regulatory T cells. $CD4^{+}CD25^{+}$ T_{Reg} cells specifically express the transcription factor forkhead box P3 (FOXP3)[85] and suppress immune responses. Studies show that the depletion of these cells can lead to autoimmunity and enhances the immune response to foreign antigens[86–89]. Interestingly, one study showed that a 12-week programme of Tai Chi Chuan exercise induced a substantial increase in circulating T_{Reg} cell numbers[22]. The production of the T_{Reg} cell-derived cytokines transforming growth factor-β (TGFβ) and IL-10 in response to *in vitro* antigenic stimulation was also markedly increased in PBMCs isolated after this exercise programme. Furthermore, a study of patients with T2D showed that regular Tai Chi Chuan exercise altered the balance between T_H1, T_H2 and T_{Reg} cell subsets by increasing FOXP3 but not TGFβ expression[90].

In a study that used a running mouse model, the responses of circulating T_{Reg} cells to moderate- or high-intensity exercise training were examined. Only the high-intensity training resulted in increases in T_{Reg} cell numbers, and it was also associated with reduced pro-inflammatory and increased anti-inflammatory cytokine expression[23]. Intriguingly, these findings imply that high-intensity exercise training might be more beneficial than moderate-intensity training in reducing the risk of chronic cardiovascular and metabolic diseases, as a result of its anti-inflammatory effects. This notion is supported by another recent study that showed that a combination of high-intensity aerobic plus resistance exercise training, in addition to daily physical activity, is required to achieve a significant anti-inflammatory effect in T2D patients[91].

Other factors. During acute exercise, there is a marked increase in the circulating levels of growth hormone, prolactin, heat shock proteins and other factors that have immunomodulatory effects by influencing leukocyte trafficking and functions[92]. Thus, these molecules may also contribute to the anti-inflammatory effects of exercise.

Taken together, these findings suggest that each bout of exercise induces an anti-inflammatory environment. Various mechanisms can contribute to this (FIG. 2), and it seems likely that their relative importance will vary depending on the frequency, intensity and duration of the exercise performed. For low-intensity exercise, such as brisk walking, it is likely that the control of body fat is the most important mechanism, but for short periods of high-intensity exercise and prolonged moderate-intensity exercise the other anti-inflammatory effects may have an increasingly important role.

The elite athlete paradox

Although regular moderate-intensity exercise is associated with a reduced incidence of upper respiratory tract infection compared with a completely sedentary state[93,94], the long hours of hard training that elite athletes undertake appears to make them more susceptible to upper respiratory tract infections[11,95–98]. This is probably attributable to the anti-inflammatory effects of exercise inducing a degree of immunosuppression[11,98], although other factors — such as psychological stress, disturbed sleep and negative energy balance — may contribute to immunosuppression in elite athletes[98]. An increased risk of minor infections may be the (small) price to be paid for the long-term health benefits of regular exercise at high dosage.

A recent murine study indicated that intensive exercise training results in an increased anti-inflammatory cytokine (IL-10) response to antigen exposure[23]. Moreover, a study on human endurance athletes revealed that whole blood cultures from athletes who were prone to illness during a 4-month period of winter training produced four times as much IL-10 following antigen stimulation as blood cultures from athletes who remained illness-free during the same period[99]. There is now extensive evidence from both murine and human studies that IL-10 production usually imposes some limits on the effectiveness of pathogen-specific immune responses, especially innate immunity and adaptive T_H1 cell responses[100,101]. These studies suggest that very high training loads induce an anti-inflammatory state that is sufficient to increase the risk of minor infections.

Conclusions and remaining questions

Regular exercise reduces the risk of chronic metabolic and cardiorespiratory diseases (TABLE 1), in part because exercise exerts anti-inflammatory effects. The anti-inflammatory effects of regular exercise may be mediated via both a reduction in visceral fat mass (with a subsequent decreased release of adipokines) and the induction of an anti-inflammatory environment with each bout of exercise. Various mechanisms may contribute to the generation of this anti-inflammatory environment, including: increased release of cortisol and adrenaline from the adrenal glands; increased production and release of IL-6 and other myokines from working skeletal muscle; reduced expression of TLRs on monocytes and macrophages (with subsequent inhibition of downstream pro-inflammatory cytokine production); inhibition of adipose tissue infiltration by monocytes and macrophages; phenotypic switching of macrophages within adipose tissue; a reduction in the circulating numbers of pro-inflammatory monocytes; and an increase in the circulating numbers of T_{Reg} cells. These anti-inflammatory effects of exercise are also likely to be responsible for the partial immunosuppression that makes elite athletes more susceptible to common infections.

At present, we do not know the relative importance of these different anti-inflammatory mechanisms, although it seems likely that this will depend on the mode, frequency, intensity and duration of the exercise performed. Intuitively, we might expect IL-6 to assume greater relative importance when the exercise is prolonged and glycogen-depleting, whereas catecholamine-mediated effects are likely to assume greater importance with shorter duration, high-intensity exercise. High training loads may be needed to increase circulating numbers of T_{Reg} cells and maximize the anti-inflammatory effects, but possibly at the cost of a small increase in infection risk. Further research should establish the mode, intensity and duration of exercise required to optimize the anti-inflammatory effects, and it still remains to be established whether exercise is always useful as a therapy for the treatment of patients with inflammation-associated disorders. Furthermore, we still need to determine the independent contribution of an exercise-induced reduction in visceral fat (versus other exercise-induced anti-inflammatory mechanisms) in reducing inflammation in adipose tissue, insulin resistance and risk of chronic disease. Although there is a consensus that exercise training protects against some types of cancer[11,102], it is not yet known whether this is due to alterations in immunological and inflammatory mechanisms. Finally, it should be noted that further research is needed to clearly demonstrate the direct and indirect molecular mechanisms by which physical exercise influences immune function. There can be no doubt that regular exercise is beneficial for health, but a major challenge is to encourage more of the general population to engage in more of it.

1. Mathis, D. & Shoelson, S. Immunometabolism: an emerging frontier. *Nature Rev. Immunol.* **11**, 81–93 (2011).
2. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, 860–867 (2006).
3. Shoelson, S. E., Lee, J. & Goldfine, A. B. Inflammation and insulin resistance. *J. Clin. Invest.* **116**, 1793–1801 (2006).
4. Ouchi, N., Parker, J. L., Lugus, J. J. & Walsk, K. Adipokines in inflammation and metabolic disease. *Nature Rev. Immunol.* **11**, 85–97 (2011).
5. Rook, G. A. & Dalgleish, A. Infection, immunoregulation, and cancer. *Immunol. Rev.* **240**, 141–159 (2011).
6. Leonard, B. E. Inflammation, depression and dementia: are they connected? *Neurochem. Res.* **32**, 1749–1756 (2007).
7. Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E. & Ridker, P. M. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* **286**, 327–334 (2001).
8. Pedersen, B. K. & Saltin, B. Evidence for prescribing exercise as therapy in chronic disease. *Scand. J. Med. Sci. Sports* **16** (Suppl. 1), 5–65 (2006).
9. Hardman, A. E. & Stensel, D. J. *Physical Activity and Health: The Evidence Explained* 2nd edn 120–121 (Routledge, Abingdon, Oxon, 2009).
10. Warren, T. Y. *et al.* Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med. Sci. Sports Exerc.* **42**, 879–885 (2010).
11. Walsh, N. P. *et al.* Position statement. Part one: immune function and exercise. *Exerc. Immunol. Rev.* **17**, 1–65 (2011).
This review provides the most up-to-date scientific consensus on the effects of exercise on immune function.
12. Jonas, S. & Phillips, E. M. *ACSM's Exercise is Medicine: A Clinician's Guide to Exercise Prescription.* (Lippincott Williams & Wilkins, Hagerstown, Maryland, 2009).

13. Kraus, W. E. *et al.* Effects of the amount and intensity of exercise on plasma lipoproteins. *N. Engl. J. Med.* **347**, 1483–1492 (2002).
14. Kasapis, C. & Thompson, P. D. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J. Am. Coll. Cardiol.* **45**, 1563–1569 (2005).
15. Petersen, A. M. & Pedersen, B. K. The anti-inflammatory effect of exercise. *J. Appl. Physiol.* **98**, 1154–1162 (2005).
16. Mathur, M. & Pedersen, B. K. Exercise as a mean to control low-grade inflammation. *Mediators Inflamm.* **2008**, 109502 (2008).
17. Flynn, M. G. & McFarlin, B. K. Toll-like receptor 4: link to the anti-inflammatory effects of exercise? *Exerc. Sport Sci. Rev.* **34**, 176–181 (2006).
18. Pedersen, B. K. & Febbraio, M. A. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol. Rev.* **88**, 1379–1406 (2008).
19. Gleeson, M., McFarlin, B. K. & Flynn, M. G. Exercise and Toll-like receptors. *Exerc. Immunol. Rev.* **12**, 34–53 (2006).
20. Kawanishi, N., Yano, H., Yokogawa, Y. & Suzuki, K. Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. *Exerc. Immunol. Rev.* **16**, 105–118 (2010).
This study demonstrates that exercise reduces inflammation in adipose tissue via two separate mechanisms.
21. Timmerman, K. L., Flynn, M. G., Coen, P. M., Markofski, M. M. & Pence, B. D. Exercise training-induced lowering of inflammatory ($CD14^+CD16^+$) monocytes: a role in the anti-inflammatory influence of exercise? *Leukoc. Biol.* **84**, 1271–1278 (2008).
22. Yeh, S.-H., Chuang, H., Lin, L.-W., Hsiao, C.-Y. & Eng, H. L. Regular tai chi chuan exercise enhances functional mobility and CD4CD25 regulatory T cells. *Br. J. Sports Med.* **40**, 239–243 (2006).
23. Wang, J. *et al.* Effect of exercise training intensity on murine T-regulatory cells and vaccination response. *Scand. J. Med. Sci. Sports* 16 Mar 2011 (doi:10.1111/j.1600-0838.2010.01288.x).
This study indicates that intensive exercise training increases circulating numbers of regulatory T cells.
24. Pischon, H. *et al.* General and abdominal adiposity and risk of death in Europe. *N. Engl. J. Med.* **359**, 2105–2120 (2008).
25. Bays, H. E. "Sick fat", metabolic disease, and atherosclerosis. *Am. J. Med.* **122**, S26–S37 (2009).
26. Haffner, S. M. Abdominal adiposity and cardiometabolic risk: do we have all the answers? *Am. J. Med.* **120**, S10–S16 (2007).
27. Whitmer, R. A. *et al.* Central obesity and increased risk of dementia more than three decades later. *Neurology* **71**, 1057–1064 (2008).
28. Xue, F. & Michels, K. B. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *Am. J. Clin. Nutr.* **86**, S823–S835 (2007).
29. Yudkin, J. S. Inflammation, obesity, and the metabolic syndrome. *Horm. Metab. Res.* **39**, 707–709 (2007).
30. Ross, R. & Bradshaw, A. J. The future of obesity reduction: beyond weight loss. *Nature Rev. Endocrinol.* **5**, 319–325 (2009).
31. Mujumdar, P. P., Duerksen, P. J., Firek, A. F. & Hessingere, D. A. Long-term, progressive, aerobic training increases adiponectin in middle-aged, overweight, untrained males and females. *Scand. J. Clin. Lab. Invest.* **71**, 101–107 (2011).
32. Ben Ounis, O. *et al.* Two-month effects of individualized exercise training with or without caloric restriction on plasma adipocytokine levels in obese female adolescents. *Ann. Endocrinol.* **70**, 235–241 (2009).
33. Lim, S. *et al.* Insulin-sensitizing effects of exercise on adiponectin and retinol-binding protein-4 concentrations in young and middle-aged women. *J. Clin. Endocrinol. Metab.* **93**, 2263–2268 (2008).
34. Mohamed-Ali, V. *et al.* Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-α, *in vivo*. *J. Clin. Endocrinol. Metab.* **82**, 4196–4200 (1997).
35. Fried, S. K., Bunkin, D. A. & Greenberg, A. S. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J. Clin. Endocrinol. Metab.* **83**, 847–850 (1998).
36. Pedersen, B. K. Edward F. Adolph Distinguished Lecture: Muscle as an endocrine organ: IL-6 and other myokines. *J. Appl. Physiol.* **107**, 1006–1014 (2009).
37. Fischer, C. P. Interleukin-6 in acute exercise and training: what is the biological relevance? *Exerc. Immunol. Rev.* **12**, 6–33 (2006).
38. Meckel, Y. *et al.* The effect of a brief sprint interval exercise on growth factors and inflammatory mediators. *J. Strength Cond. Res.* **23**, 225–230 (2009).
39. Keller, C. *et al.* Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. *J. Appl. Physiol.* **99**, 2075–2079 (2005).
40. Pedersen, B. K. & Fischer, C. P. Beneficial health effects of exercise — the role of IL-6 as a myokine. *Trends Pharmacol. Sci.* **28**, 152–156 (2007).
This is an important review that introduces the concept of skeletal muscle acting as an endocrine organ.
41. Steensberg, A., Fischer, C. P., Keller, C., Moller, K. & Pedersen, B. K. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am. J. Physiol. Endocrinol. Metab.* **285**, E433–E437 (2003).
42. Starkie, R., Ostrowski, S. R., Jauffred, S., Febbraio, M. & Pedersen, B. K. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-α production in humans. *FASEB J.* **17**, 884–886 (2003).
43. Freeman, B. D. & Buchman, T. G. Interleukin-1 receptor antagonist as therapy for inflammatory disorders. *Expert Opin. Biol. Ther.* **1**, 301–308 (2001).
44. Maynard, C. L. & Weaver, C. T. Diversity in the contribution of IL-10 to cell-mediated immune regulation. *Immunol. Rev.* **226**, 219–233 (2008).
45. Moore, K. W., de Waal Malefyt, R., Coffman, R. L. & O'Garra, A. Interleukin-10 and the interleukin-10 receptor. *Annu. Rev. Immunol.* **19**, 683–765 (2001).
46. Hong, E. G. *et al.* Interleukin-10 prevents diet-induced insulin resistance by attenuating macrophage and cytokine response in skeletal muscle. *Diabetes* **58**, 2525–2535 (2009).
47. Miyashita, M., Burns, S. F. & Stensel, D. J. Accumulating short bouts of brisk walking reduces postprandial plasma triacylglycerol concentrations and resting blood pressure in healthy young men. *Am. J. Clin. Nutr.* **88**, 1225–1231 (2008).
48. Murphy, M., Nevill, A., Neville, C., Biddle, S. & Hardman, A. E. Accumulating brisk walking for fitness, cardiovascular risk, and psychological health. *Med. Sci. Sports Exerc.* **34**, 1468–1474 (2002).
49. Galbo, H. *Hormonal and Metabolic Adaptation to Exercise* (Georg Thieme Verlag, Stuttgart, 1983).
50. Cupps, T. R. & Fauci, A. S. Corticosteroid-mediated immunoregulation in man. *Immunol. Rev.* **65**, 133–155 (1982).
51. Bergmann, M. *et al.* Attenuation of catecholamine-induced immunosuppression in whole blood from patients with sepsis. *Shock* **12**, 421–427 (1999).
52. Jiao, P. *et al.* Obesity-related upregulation of monocyte chemotactic factors in adipocytes: involvement of nuclear factor-κB and c-Jun NH_2-terminal kinase pathways. *Diabetes* **58**, 104–115 (2009).
53. Kim, D. H. *et al.* The role of GM-CSF in adipose tissue inflammation. *Am. J. Physiol. Endocrinol. Metab.* **295**, E1038–E1046 (2008).
54. Kanda, H. *et al.* MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J. Clin. Invest.* **116**, 1494–1505 (2006).
55. Xu, H. *et al.* Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* **112**, 1821–1830 (2003).
56. Gautier, E. L., Jakubzizk, C. & Randolph, G. J. Regulation of the migration and survival of monocytes subsets by chemokine receptors and its relevance to atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **29**, 1412–1418 (2009).
57. Zeyda, M., Huber, J., Prager, G. & Stulnig, T. M. Inflammation correlates with markers of T-cell subsets including regulatory T cells in adipose tissue from obese patients. *Obesity* **19**, 743–748 (2011).
58. Cinti, S. *et al.* Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J. Lipid Res.* **46**, 2347–2355 (2005).
59. Bruun, J. M., Lihn, A. S., Pedersen, S. B. & Richelsen, B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophages resident in the AT. *J. Clin. Endocrinol. Metab.* **90**, 2282–2289 (2005).
60. Bishop, N. C., Walker, G. J., Gleeson, M., Wallace, F. A. & Hewitt, C. R. A. Human T lymphocyte migration towards the supernatants of human rhinovirus infected airway epithelial cells: influence of exercise and carbohydrate intake. *Exerc. Immunol. Rev.* **15**, 42–59 (2009).
61. Bermon, S. Airway inflammation and upper respiratory tract infection in athletes: is there a link? *Exerc. Immunol. Rev.* **13**, 6–14 (2007).
62. Maffei, M. *et al.* The obesity and inflammatory marker haptoglobin attracts monocytes via interaction with chemokine (C-C motif) receptor 2 (CCR2). *BMC Biol.* **17**, 87 (2009).
63. Nara, N. *et al.* Disruption of CXC motif chemokine ligand-14 in mice ameliorates obesity-induced insulin resistance. *J. Biol. Chem.* **282**, 30794–30803 (2007).
64. Bosanská, L. *et al.* The influence of obesity and different fat depots on adipose tissue gene expression and protein levels of cell adhesion molecules. *Physiol. Res.* **59**, 79–88 (2010).
65. Chow, F. Y., Nikolic-Paterson, D. J., Ozols, E., Atkins, R. C. & Tesch, G. H. Intercellular adhesion molecule-1 deficiency is protective against nephropathy in type 2 diabetic db/db mice. *J. Am. Soc. Nephrol.* **16**, 1711–1722 (2005).
66. Zoppini, G. *et al.* Effects of moderate-intensity exercise training on plasma biomarkers of inflammation and endothelial dysfunction in older patients with type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* **16**, 543–549 (2006).
67. Martinez, F. O., Sica, A., Mantovani, A. & Locati, M. Macrophage activation and polarization. *Front. Biosci.* **13**, 453–461 (2008).
68. Lumeng, C. N., Bodzin, J. L. & Saltiel, A. R. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J. Clin. Invest.* **117**, 175–184 (2007).
This study demonstrates that obesity leads to a shift in adipose tissue macrophage polarization from an alternatively activated state to a classically activated (more pro-inflammatory) state.
69. Kaisho, T. & Akira, S. Toll-like receptor function and signalling. *J. Allergy Clin. Immunol.* **117**, 979–987 (2006).
70. Takeda, K., Kaisho, T. & Akira, S. S. Toll-like receptors. *Annu. Rev. Immunol.* **21**, 335–376 (2003).
71. Lancaster, G. I. *et al.* The physiological regulation of Toll-like receptor expression and function in humans. *J. Physiol.* **563**, 945–955 (2005).
This was the first study to show that acute exercise causes a downregulation of TLR expression on circulating monocytes and their downstream functional responses.
72. Oliveira, M. & Gleeson, M. The influence of prolonged cycling on monocyte Toll-like receptor 2 and 4 expression in healthy men. *Eur. J. Appl. Physiol.* **109**, 251–257 (2010).
73. Stewart, L. K. *et al.* Influence of exercise training and age on $CD14^+$ cell surface expression of Toll-like receptor 2 and 4. *Brain Behav. Immunol.* **19**, 389–397 (2005).
This paper reports that exercise training is associated with a reduction in TLR expression on circulating monocytes in humans.
74. Nguyen, M. T. *et al.* A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. *J. Biol. Chem.* **282**, 35279–35292 (2007).
75. Starkie, R., Ostrowski, S. R., Jauffred, S., Febbraio, M. & Pedersen, B. K. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-α production in humans. *FASEB J.* **17**, 884–886 (2003).
76. Skinner, N. A., MacIsaac, C. M., Hamilton, J. A. & Visvanathan, K. Regulation of Toll-like receptor (TLR)2 and TLR4 on $CD14^{dim}CD16^+$ monocytes in response to sepsis-related antigens. *Clin. Exp. Immunol.* **141**, 270–278 (2005).
77. Belge, K. U. *et al.* The proinflammatory $CD14^+CD16^+DR^{++}$ monocytes are a major source of TNF. *J. Immunol.* **168**, 3536–3542 (2002).
78. Baeten, D. *et al.* Human cartilage $gp39^+$, $CD16^+$ monocytes in peripheral blood and synovium: correlation with joint destruction in rheumatoid arthritis. *Arthritis Rheum.* **43**, 1233–1243 (2000).
79. Schlitt, A. *et al.* $CD14^+CD16^+$ monocytes in coronary artery disease and their relationship to serum TNF-α levels. *Thromb. Haemost.* **92**, 419–424 (2004).

80. Giulietti, A. *et al.* Monocytes from type 2 diabetic patients have a pro-inflammatory profile: 1,25-dihydroxyvitamin D_3 works as anti-inflammatory. *Diabetes Res. Clin. Pract.* **77**, 47–57 (2007).
81. Simpson, R. J. *et al.* Toll-like receptor expression on classic and pro-inflammatory blood monocytes after acute exercise in humans. *Brain Behav. Immunol.* **23**, 232–239 (2009).
82. Fingerle-Rowson, G., Angstwurm, M., Andreesen, R. & Ziegler-Heitbrock, H. W. Selective depletion of $CD14^+CD16^+$ monocytes by glucocorticoid therapy. *Clin. Exp. Immunol.* **112**, 501–506 (1998).
83. Viswanathan, K. & Dhabhar, F. S. Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. *Proc. Natl Acad. Sci. USA* **102**, 5808–5813 (2005).
84. Keylock, K. T. *et al.* Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. *Am. J. Physiol.* **294**, R179–R184 (2008).
85. Sakaguchi, S. Naturally arising Foxp3-expressing $CD25^+CD4^+$ regulatory T cells in immunological tolerance to self and non-self. *Nature Immunol.* **6**, 345–352 (2005).
86. Fernandez, M. A. *et al.* T regulatory cells contribute to the attenuated primary $CD8^+$ and $CD4^+$ T cell responses to herpes simplex virus type 2 in neonatal mice. *J. Immunol.* **180**, 1556–1564 (2008).
87. Furuichi, Y. *et al.* Depletion of $CD25^+CD4^+$ T cells (Tregs) enhances the HBV-specific $CD8^+$ T cell response primed by DNA immunization. *World J. Gastroenterol.* **11**, 3772–3777 (2005).
88. Nakahara, M. *et al.* The effect of regulatory T-cell depletion on the spectrum of organ-specific autoimmune diseases in nonobese diabetic mice at different ages. *Autoimmunity* 9 Feb 2011 (doi:10.3109/08916934.2010.548839).
89. Paust, H. J. *et al.* Regulatory T cells control the Th1 immune response in murine crescentic glomerulonephritis. *Kidney Int.* **80**, 154–164 (2011).
90. Yeh, S. H. *et al.* Regular Tai Chi Chuan exercise improves T cell helper function of patients with type 2 diabetes mellitus with an increase in T-bet transcription factor and IL-12 production. *Br. J. Sports Med.* **43**, 845–850 (2009).
91. Balducci, S. *et al.* Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch. Intern. Med.* **170**, 1794–1803 (2010).
92. Pedersen, B. K. & Hoffman-Goetz, L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol. Rev.* **80**, 1055–1081 (2000).
93. Matthews, C. E. *et al.* Moderate to vigorous physical activity and risk of upper-respiratory tract infection. *Med. Sci. Sports Exerc.* **34**, 1242–1248 (2002).
94. Nieman, D. C., Henson, D. A., Austin, M. D. & Sha, W. Upper respiratory tract infection is reduced in physically fit and active adults. *Br. J. Sports Med.* 1 Nov 2010 (doi:10.1136/bjsm.2010.077875). **References 93 and 94 show that regular moderate exercise reduces the incidence of upper respiratory tract infections in humans.**
95. Bishop, N. C. in *Immune Function in Sport and Exercise* (ed. Gleeson, M.) 1–14 (Elsevier, Edinburgh, 2005).
96. Fahlman, M. M. & Engels, H. J. Mucosal IgA and URTI in American college football players: a year longitudinal study. *Med. Sci. Sports Exerc.* **37**, 374–380 (2005).
97. Nieman, D. C., Johanssen, L. M., Lee, I. W. & Arabatzis, K. Infectious episodes in runners before and after the Los Angeles marathon. *J. Sports Med. Phys. Fitness* **30**, 316–328 (1990).
98. Gleeson, M. Exercise and immune function. *J. Appl. Physiol.* **103**, 693–699 (2007).
99. Gleeson, M. *et al.* Respiratory infection risk in athletes: association with antigen-stimulated IL-10 production and salivary IgA secretion. *Scand. J. Med. Sci. Sports* 8 Mar 2011 (doi:10.1111/j.1600-0838.2010.01272.x). **This study showed that illness-prone athletes had higher levels of IL-10 production in whole blood culture in response to *ex vivo* antigen stimulation.**
100. van der Sluijs, K. F. IL-10 is an important mediator of the enhanced susceptibility to pneumococcal pneumonia after influenza infection. *J. Immunol.* **172**, 7603–7609 (2004).
101. Blackburn, S. D. & Wherry, E. J. IL-10, T cell exhaustion and viral persistence. *Trends Microbiol.* **15**, 143–146 (2007).
102. Thune, I. & Furberg, A. S. Physical activity and cancer risk: dose–response and cancer, all sites and site-specific. *Med. Sci. Sports Exerc.* **33**, S530–S550 (2001).
103. Gill, J. M. R. & Cooper, A. R. Physical activity and prevention of type 2 diabetes mellitus. *Sports Med.* **38**, 807–824 (2008).
104. Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* **344**, 1343–1350 (2001).
105. Eriksson, K. F. & Lindgärde, F. Prevalence of type 2 (non-insulin dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmö feasibility study. *Diabetologia* **34**, 891–898 (1991).
106. Church, T. S. *et al.* Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* **27**, 83–88 (2004).
107. Tanasescu, M., Leitzmann, M. F., Rimm, E. B. & Hu, F. B. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* **107**, 2435–2439 (2003).
108. Donath, M. Y. & Shoelson, S. E. Type 2 diabetes as an inflammatory disease. *Nature Rev. Immunol.* **11**, 98–107 (2011).
109. Tanasescu, M. *et al.* Exercise type and intensity in relation to coronary heart disease in men. *JAMA* **288**, 1994–2000 (2002).
110. Eliassen, H. A., Hankinson, S. E., Rosner, B., Holmes, M. D. & Willet, W. C. Physical activity and risk of breast cancer among postmenopausal women. *Archiv. Int. Med.* **170**, 1758–1764 (2010).
111. Wolin, K. Y., Yan, Y. & Colditz, G. A. Physical activity and risk of colon adenoma: a meta-analysis. *Br. J. Cancer* **104**, 882–885 (2011).
112. Abbott, R. D. *et al.* Walking and dementia in physically capable elderly men. *JAMA* **292**, 1447–1453 (2004).
113. Bishop, N. C. & Gleeson, M. Acute and chronic effects of exercise on markers of mucosal immunity. *Front. Biosci.* **14**, 4444–4456 (2009).

Competing interests statement
The authors declare no competing financial interests.

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