

## **Physical and immunological aspects of exercise in chronic diseases**

**Vasso Apostolopoulos<sup>1,2,#</sup>, Erika Borkoles<sup>3</sup>, Remco Polman<sup>3</sup>, Lily Stojanovska<sup>1,#</sup>**

<sup>1</sup> *College of Health and Biomedicine, Centre for Chronic Disease Prevention and Management, Victoria University, PO Box 14428, Melbourne, Victoria 8001, Australia*

<sup>2</sup> *VAConsulting Services, PO Box 6437, Melbourne Victoria 3030, Australia*

<sup>3</sup> *College of Sport & Exercise Science, Victoria University, PO Box 14428, Melbourne, Victoria 8001, Australia*

<sup>#</sup> *Authors for correspondence: vasso@scientist.com and Lily.Stojanovska@vu.edu.au*

**Running Title:** Exercise to boost immunity

**Background:** Physical inactivity and sedentary lifestyles are believed to be independent risk factors for the occurrence of numerous diseases, including, obesity, type-2 diabetes, metabolic syndrome, cardiovascular disease, cancer and mental health, all leading to substantial morbidity and/or premature death. It has been found that regular exercise, is associated with better quality of life and health outcomes, and reduces the risk of cardiovascular disease and cancer. Here, we review the effects regular exercise has on mental health and well-being, on the immune system and in cancer, cardiovascular disease, autoimmunity and metabolic syndrome. Is exercise the new immunotherapy to treat diseases?

**KEYWORDS:** cancer . chronic diseases . exercise . immune status . immunity, immunotherapy . inflammation . physical activity

## **Introduction**

Physical inactivity is ranked just behind cigarette smoking as a contributing factor of lifestyle health issues and conditions [1]. Physical inactivity is a ‘health hazard’. Physical activity and exercise, on the otherhand, appears to be a cost-effective immunotherapeutic approach with few known side effects. Most importantly, people with greater levels of physical activity report improvements in mental and physical health, as well as quality-of-life [2-5]. Such improvements can even be achieved with low intensity aerobic activity, such as walking and dancing [6]. According to the Global Recommendations on physical activity for health, released by the World Health Organisation in 2011, 150 minutes a week of moderate physical activity can reduce the risk of breast and colon cancers, diabetes and heart disease [7]. However, this was recently updated (06 February 2014) by the Department of Health, Australia. This suggests that we should accumulate 150-300 minutes a week of moderate intensity physical activity, or 75-150 minutes of vigorous intensity physical activity to be undertaken per week for health. In addition, strength training should be included at least 2 days per week [8], in order to build bone and muscle strength, aid in body fat burn and increase in metabolism, for 18-64 year olds [8].

## **The benefits of exercise to health**

As early as the 5<sup>th</sup> century BC, exercise was recognized to be the best medicine for health and wellbeing. Hippocrates stated..., “All parts of the body, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are unused and left idle, they become liable to disease, defective in growth and age quickly”. However, the importance of physical activity waned with the decline of ancient civilization and until a decade ago, physical activity was predominantly used in military, sports and athletics. The important observational studies of Jerry Morris et al, in the 1940s-1950s, changed modern views of exercise, fitness and health, even though the scientific community did not readily accept

these [9]. In 1949, Morris and colleagues noticed that double decker bus drivers had higher rates of cardiovascular disease compared to the conductors who climbed the stairs of the bus [10]. Overall the conductors had lower blood pressure and wore smaller uniform sizes as compared to the drivers. In addition, postmen that rode their bike, had lower incidence of heart attacks compared to those who worked at sedentary jobs, such as clerks or telephone receptionists [11]. Further studies demonstrated that gardening did not have the same effects on heart disease as did exercise or more vigorous physical activity [12]. These studies led to the importance of physical activity with a link to health outcomes. With the exponential number of publications and correlations of physical activity in health and disease prevention in the last decade, a new era has evolved between the relationship of exercise and health and wellbeing.

Physical inactivity and sedentary lifestyles are believed to be independent risk factors for the occurrence of obesity, type-2 diabetes and metabolic syndrome [13]. Visceral fat activates a range of inflammatory pathways that leads to insulin resistance and atherosclerosis. These diseases are commonly referred to as, 'sedentariness'. As such, lifelong physical activity, or beginning physical activity at any stage of life, results in significant cardiovascular health benefits [14]. Modern lifestyles, have forced people to be less active, as much time is spent watching television, searching the internet, electronic game playing and reading. The amount of time spent being physically inactive predicts ill health [15]. For instance, a large longitudinal Canadian study of 17,013 people over 12 years, demonstrated that those who were inactive for a longer block of time were 50% more likely to die prematurely compared to those who sat for shorter periods of time [16]. Interestingly, there was a dose response relationship between total sitting time and ill health, ie. the longer one sat, the more likely they were to experience ill health, independently of the amount of physical activity. Hence, the time we spend sitting and its distribution throughout the day, rather than being less or more physically active, is associated with increased morbidity and mortality. In fact, the Department of Health Australia, suggests to, 'minimise the amount of time spent in prolonged sitting', and to 'break up long periods of sitting as often as possible' [8]. In the last 2 decades, there has been an explosion in diseases associated with inactivity. A dose response relationship exists indicating that people with high physical activity have the lowest risk factor for premature death. Regular exercise, either as part of a lifestyle or as part of a disease intervention program are associated with better physical and mental health outcomes, to chronic diseases, such as, cancer, obesity, osteoporosis, stroke, coronary heart disease (CHD), cardiovascular disease (CVD), blood pressure, type-2 diabetes, cognitive functioning and mental health and well-being [17-20]. However, high physical activity increases the risk of injury, hence, extra care should be taken when increasing physical activity.

### **Exercise, the immune system and disease**

Exercising on a regular basis is one of the pillars of leading a healthy lifestyle. Regular exercise is known to improve cardiovascular health [21], lowers blood pressure [22], helps control body weight, and protects against a variety of diseases. But does it help maintain a healthy immune system? Just like a healthy diet, exercise can contribute to general good health and therefore to a healthy immune system. Indeed, western diet, stress, smoking, sleep deprivation and inactivity, have all been linked to immune system

disorders and chronic inflammation [23]. Hence, it is conceivable to include exercise in daily routines for immunological health benefit.

#### **a. Exercise and immune cells**

Brief exercise is known to induce a stress response and increases inflammatory cells in the circulation, including monocytes [24]. Exercise affects monocyte (CD14+) phenotype, cell surface markers, cytokine secretion, increases the number of circulatory monocytes of up to 4.8 fold, and cortisol released during exercise up-regulates monocyte CCR2 expression and migration activity [25]. Dendritic cells (DC) (MHC class II expression, mixed lymphocyte reaction and IL-12 production) and neutrophils are also increased in the circulation during exercise [26]. In addition, during brief exercise, natural killer (NK) cells are increased up to 5-fold in blood, which play a role in defense against pathogens and cancer immunosurveillance [27]. However, after prolonged exercise, the number of NK cells are reduced [26]. NK cells are the most sensitive population of immune cells to exercise stress. A short bout of 30 minutes of cycling increases the expression of cytokines of, T-cells (TNF-alpha, IL-6, IL-4), of monocytes (IFN-gamma, IL-4), and, of B-cells (GH, IGF-I) [28]. At the molecular level, it is becoming clear that exercise does not change cell surface markers, but instead selectively mobilises subsets of cells that have pre-determined levels of these markers [29, 30].

A study consisting of 12 healthy males aged in their 20s underwent 10 x 2 minute bouts of cycle ergometer exercise (high intensity exercise training or HIT) equivalent to 82% of peak  $VO_2$  consumption followed by a 1 minute rest [24]. Immediately following exercise peripheral blood mononuclear cells (PBMC) were isolated and using gene arrays, gene alterations were noted which were likely to direct monocytes into an anti-inflammatory pathway [24]. Down-regulation of monocyte tumor necrosis factor (TNF), toll-like receptor-4 (TLR4) and CD36 genes and up-regulation of EREG and CXCR4 were noted, which influence vascular health. Hence, despite the stress response induced by HIT exercise, this stress response has a positive outcome that appears to promote cardiovascular health. Likewise, TLR-2 and HLA-DR expression were down-regulated, which may have implications for modulation of post-exercise immune surveillance [31]. In addition, in patients with high blood pressure, exercise increases the expression of monocyte CD62L and CXCR2. However, the clinical implications of this response need to be further examined [32]. In a similar study, consisting of 13 healthy males aged in their 20s underwent a similar HIT exercise regime, 10 x 2 minute bouts of cycle ergometer exercise equivalent to 77% of  $VO_{2max}$  followed by a 1 minute rest [27]. NK cells isolated from PBMC and using gene arrays, it was found that 986 genes and gene pathways were altered, predominantly those involved with cancer, (melanoma, glioma, prostate cancer), p53 signaling pathway, cell to cell communication, focal adhesion and adherens junction [27]. This data supports that even brief bouts of high intensity exercise alters the expression of NK cell genes and this could alter health through the innate immune system. A similar exercise regime was applied to 11 healthy males aged in their 20s who performed 10 x 2 minute bouts of cycle ergometer exercise equivalent to 76% of  $VO_{2max}$  followed by a 1 minute rest [24]. Immediately following exercise, neutrophils were isolated and using gene arrays and in silico analysis, 4,724 genes and 3 pathways were altered; Ubiquitin-mediated proteolysis, Jak-STAT signaling pathway and Hedgehog signaling pathway [24]. These pathways are known to play a role in inflammation in humans. Similarly, pro-inflammatory (IL-32, TNFSF8 and CCR5), anti-inflammatory (ANXA1), growth and repair genes (AREG and FGF2, involved in angiogenesis) and genes known

to be involved in asthma and arthritis, were altered following exercise [33]. In sedentary women, a single bout of cycling, for 1 hour, increased the phagocytic and oxygen-dependent microbial capacity of neutrophils [34]. It is clear that in particular aerobic exercise of different durations and intensities has a direct impact on immune cells. These responses appear to have beneficial outcomes to disease.

### **b. Exercise and anti-inflammatory effects**

Low-grade chronic inflammation is involved in atherosclerosis, diabetes and chronic pathological diseases. Regular physical activity reduces the risk of chronic diseases, partly due to the anti-inflammatory effects of exercise [35]. These effects may be mediated via reduction in visceral fat mass and decreased adipokines secretion, and an altered inflammatory milieu following exercise [35]. Physical activity reduces IL-6, IL-8 and IL-15 cytokines and during muscle contractions, IL-1 receptor antagonists and TNF-receptor molecules are released which have anti-inflammatory effects [36]. Inflammatory cytokines are also associated with age and diseases related to inactivity. In a group of 65-80 year old females, those assigned to exercise training for 12 weeks were associated with lower levels of monocytes and TNF-alpha production [37]. In addition, moderate to high intensity training, reduces systemic cytokines (TNF-alpha, IL-6, IL-1beta) in an inflammatory milieu in elderly women [38], and in obesity [39]. Further, CRP is significantly decreased in physically active subjects [40], and growth hormone secretagogue receptor-1a is increased which has high anti-inflammatory properties [41]. These studies suggest that exercise has anti-inflammatory effects.

In animal models, rats subjected to treadmill exercise decreases oxidative stress (malondialdehyde), CRP and proteinuria [42]. Further, increase in antioxidant enzyme (superoxide dismutase), Cu/Zn superoxide dismutase protein in renal proximal tubules, nuclear levels of Nrf2 transcription factor D1 receptor function and IL-10 cytokines are noted in rats undergoing exercise as compared to sedentary rats [42]. Exercise may therefore be beneficial in preventing oxidative stress, inflammation and preserving kidney function. Interestingly, moderate aerobic exercise of mice, decreases Th2 responses and Th cell migration within the lungs of an ovalbumin (OVA)-sensitized murine allergic asthma model [43], as well as decreasing leukocyte infiltration and activation of NF- $\kappa$ B [44]. In addition, forced treadmill running exacerbates inflammation, by increasing diarrhea, IL-6, IL-1beta, IL-17, however, voluntary treadmill running attenuated symptoms of inflammation in a colitis mouse model [45]. Further, intense aerobic treadmill exercise increases pro-TNF-alpha and anti-IL-10 and pro-apoptotic protein (caspase 3), indicating an overall anti-inflammatory effect as a result of wheel running in healthy mice [46]. Likewise, exhaustive exercise reduces TNF-alpha and IFN-alpha concentrations and this reduction is via TLR-7 and elevation of systemic catecholamines [47]. Further, hepatic inflammation and fibrosis is reduced by reduction of TNF-alpha, macrophage infiltration and tissue inhibitor of matrix metalloproteinase-1 mRNA [48]. It is clear that factors released by exercise, such as IL-6 and decreasing levels of TNF-alpha production, lead to a decreased inflammatory state.

### **c. Keeping the metabolic balance through exercise**

An increase in sedentary lifestyles with decreasing physical activity has led to obesity, type-2 diabetes, hypertension, hypercholesterolemia and metabolic syndrome factors [49]. These constitute the metabolic syndrome, leading to atherosclerosis and other cardiovascular related diseases. It is believed that high calorie intake plays a role,

however, there is evidence supporting that, adequate physical activity reduces the risks without the need to modify caloric intake to keep a metabolic balance. In fact, exercise has been shown to reverse the risk of developing metabolic syndrome in those with high-fat diets [50]. In addition, the Amish community, which has maintained a physically active lifestyle, has much lower prevalence of type-2 diabetes and obesity despite high calorie intake [51]. Further, a few days of bed-rest (inactivity) in healthy individuals results in decreased effects of insulin and glucose utilization, despite normal diet [52]. A 28 year study, from 1970-1998, involving 2,501 healthy males demonstrated that physical activity (daily walking, gardening or cycling) inversely correlated to weight gain [53], and those with high intensity activity had greater health benefits.

Wild animals do not suffer from metabolic diseases due to their 'continuous' physically active state. Physical activity and exercise, attenuates high blood pressure, insulin resistance, glucose intolerance, cholesterol, triglyceride and obesity [54]. In a 12 week trial of obese middle-aged women taking part in a 1 hour resistance and aerobic exercise, 3 days per week clearly demonstrated that metabolic syndrome factors (blood pressure, percent body fat, fasting glucose levels, triglyceride and cholesterol levels) and, visfatin levels, were significantly lowered [55]. Blood pressure is lower in physically active women compared to healthy sedentary women [56], and, resistance training for 12 weeks improves heart rate, blood pressure and cholesterol levels [57]. In addition, aerobic exercise improves metabolic syndrome factors such as, blood pressure, waist circumference, and fasting glucose levels [58], and, protects against obesity related low-grade inflammation and beta-adrenergic receptor desensitization [59]. In addition, Bikram yoga 3 times per week, improves glucose tolerance in older obese adults [60], improves arterial stiffness and insulin resistance in adults [61], and, resistance exercise significantly decreases triglyceride values [62]. Furthermore, a 10 year study, involving 4,100 males and 963 females, indicated that the ones that were involved in walking, running, jogging, treadmill type exercises, were associated with lower body mass index and triglyceride levels as compared to the ones that did not undertake regular exercise over the 10 year period [63].

Several chronic conditions, including those related to the metabolic syndrome are orchestrated by inflammatory cytokines. As such, TNF-alpha is increased in chronic conditions such as type-2 diabetes, obesity and atherosclerosis (reviewed in [44]). TNF-alpha plays a role in insulin resistance and has been suggested as an intermediary link between obesity and inflammatory diseases including heart disease and type-2 diabetes [44]. Numerous studies suggest that increasing physical activity is effective in reducing low-level inflammation. For example, diabetic or metabolic syndrome males put on a 3-week daily exercise program showed significant reductions in body mass index, serum lipids and cholesterol, fasting glucose, insulin, macrophage inflammatory protein-1alpha, matrix metalloproteinase-9 and C-reactive protein (CRP) [64, 65]. Moreover, voluntary habitual exercise augments the innate immune system, through increases in stress-evoked heat shock protein 72 (Hsp72), MCP-1, IL-6 and IL-10 and decreases inflammatory cytokines IL-1 beta and TNF-alpha [66]. In addition, soluble intercellular adhesion molecule-1 (sICAM-1) levels are significantly improved in physically active type-2 diabetic patients [67]. Exercise also up-regulates peroxisome proliferator-activated receptor-gamma (PPAR-gamma) in the plasma and on monocytes [68]. Myokines, such as IL-6 are released by muscle cells during exercise, which further have anti-inflammatory effects [69]. Hence, exercise reduces oxidative stress, inflammation and monocyte-endothelial interactions, and increases PPAR-gamma and myokines, all of which have

been linked to have anti-diabetic and anti-metabolic syndrome effects. Major lifestyle changes like increasing physical activity habits, may therefore improve patients with diabetes or metabolic syndrome factors and in patients with coronary arterial disease risk factors. Even in those who feel too ill to exercise, decreasing sedentariness is clearly a positive start. In postmenopausal women for example, cardiovascular disease is increased, and this risk is significantly lowered in physically active women [56], by improving antioxidant capacity and decreasing body iron burden [70]. Physical activity plays a pivotal role in maintaining health and metabolic balance. Indeed, the National and Nutrition Examinations Study (NHANES III) [71, 72], concluded that physical activity is the primary element to prevent and treat metabolic syndrome.

#### **d. Reducing the risk of Cardiovascular disease through exercise**

CVD, a disease of the heart or blood vessels, and includes conditions such as CHD, atherosclerosis, ischemic stroke, hypertension, myocardial infarction and sudden cardiac death. Studies have demonstrated an association between physical activity with all-cause cardiovascular mortality and prevention of CHD [73]. In 1992, the American Heart Association recognised that physical inactivity to be a 'risk factor' for CHD and CVD [74], and in 1996 a report from the Surgeon general was published which indicated that 'regular physical activity decreases the risk of CHD and CVD' [75]. The US department of health and human services, issued the first physical activity guidelines in 2008 [76] which was based on published research studies between 1995-2007, on the effects of physical activity with CHD risk, and conducted in numerous countries (USA, UK, Norway, Finland, Canada, Sweden, Israel), and included over 453,000 subjects, both males and females and different racial backgrounds (reviewed in, [77]). Regular exercise training and improvements in cardiorespiratory fitness, reduces CVD risks [78].

Atherosclerosis is characterized by endothelial dysfunction, increase in oxidised stress, accumulation of lipids on blood vessel walls and inflammation. Physical activity can prevent and/or attenuate atherosclerosis by correcting and preventing endothelial dysfunction. Patients with coronary artery disease could be reversed with exercise training, by reversing endothelial dysfunction and improvement of blood flow of the coronary artery [79]. In a 5-year randomised trial of 73 males aged 70 years or less with chronic heart failure, were assigned ergometer exercise in the hospital 4-6 times per day for 2 weeks followed by 6-months at home ergometer exercise training of 20 minutes per day. After 6 months, patients in the exercise group had improvements in maximal ventilation, exercise time, resting heart rate, stroke volume at rest and reduction in cardiomegaly [80]. A recent long term 25 year study, assessing the effects of physical activity over 25 years on atherosclerosis in 101 middle aged men, demonstrated that regular high to very high physical activity had better outcomes in regards to cardiometabolic profiles (coronary artery calcification, carotid intima-media thickness and reactive hyperemia index) as compared to men with lower physical activity [81]. Similarly, 4 weeks of high intensity exercise training in coronary artery disease patients, significantly improved maximal work capacity, lipid profile, body mass index, blood pressure, fasting glucose, hemoglobin A1c and was associated with reduced CD11b and VLA-4 (CD49d) [82]. Furthermore, monocyte activation and transendothelial migration changes result after short-term exercise in an intensity-dependent manner (light, moderate, high) [83]. Moreover, aerobic exercise, but not resistance exercise, reduces CRP, IL-18 and IL-6, all markers of inflammation which are mediators associated with numerous diseases including atherosclerosis and hypertension [84, 85]. Thus, regular high intensity physical

activity may protect against atherosclerosis. Indeed, it is suggested to expend at least 1,500 calories per week to halt atherosclerosis process and 2,200 calories per week for stenosis regression [86].

An early indicator of atherosclerosis is the decreased nitric oxide (NO) bioactivity, which plays a role in oxidation of LDL-cholesterol. Inactivation of NO and high levels of reactive oxygen species (ROS) are present in patients with CVD, atherosclerosis and coronary arterial disease [87]. Patients with acute myocardial infarction, participating in short term low intensity exercise (use of treadmill in the hospital), have no changes in ROS, or NO, but show improved physical capacity, lower blood pressure [88], enhanced quality of life, and positive outcomes to morbidity and mortality [89]. However, the intensity of exercise impacts the oxidized-LDL (a stimulator of oxidative stress)-mediated status of monocytes. High intensity exercise increases oxidized-LDL-induced monocyte ROS production, facilitating monocyte-related atherogenesis. However this was depressed by mild to moderate exercise, indicating that lower intensity exercise may protect against suppression of anti-oxidative capacity of monocyte by oxidized-LDL [90]. It is clear that exercise has benefits for cardiovascular health with marked reductions in the long term-risk of CVD and mortality. Even in obese patients, or patients with several risk factors of CVD, regular exercise provides considerable CVD protection [91]. CVD patients frequently use the term 'I do not have enough time for exercise' or are they in fact afraid that exercise would do damage rather than good? In a HIT study in patients with chronic heart failure, it was shown to effectively reduce blood pressure and improve insulin resistance without any danger to the patient [92]. Understanding the risks and benefits of exercise to CVD patients and to the general population should be implemented for disease treatment and prevention.

#### **e. Exercise and Psychological factors**

Psychological factors can influence physical health, either indirectly, such as eating, sleeping and socializing changes, or directly, by changes in heart rate or hormones. A number of psychological factors influence the body leading to, stress, mental health problems, depression, anxiety, insomnia, alcohol and drug misuse or psychosis. Increasing data have demonstrated the role of physical activity and exercise in improving psychological risk factors and stress-related mortality [93]. In a national Canadian health survey of mental health and well-being (CCHS 1.2) representing 25 million people aged over 15 years, concluded that physical inactivity was a significant risk factor for common mental disorders, with 780,000 cases being attributed to physical inactivity [4].

An analysis based on 80 studies demonstrated a positive correlation between physical activity and clinical depression, regardless of gender, age or health status [94], and regular exercise by patients after termination of anti-depressants, had lower depression scores than those who were sedentary [2]. A study involving 950 males and 1,045 females (mean age 31.5 years) presenting with major depression, demonstrated that those that undertook physical activity improved in their depressive state overall. Males significantly improved in insomnia, fatigue and suicidality and females improved in hypersomnia, irrational guilt, vacillating thoughts and suicidality, compared to inactive control subjects [95]. On the whole regular physical activity participation results in enhanced psychological well-being. This includes improved mood, self-esteem and reduced anxiety, and stress [3], and subsequent prognosis. Even a single bout of walking induces beneficial psychological effects (tension, anxiety, anger, hostility, confusion) in elderly women [96]. In addition, in pregnant women, a single exercise class, improves the



emotional state significantly [97], and no difference in mood outcomes were noted whether aqua exercise or studio gym exercise was used [98]. Increasing evidence indicates that there are various interactions between the nervous system and the immune system, and the important role the immune system plays in the pathogenesis of depression. Pro-inflammatory cytokines (IL-1, TNF-alpha) have been implicated in being involved in the neurobiological manifestations of depression. IL-6 is both a pro-inflammatory and an anti-inflammatory cytokine, which has inhibitory effects on the pro-inflammatory cytokines TNF-alpha and IL-1. Interestingly, physical activity changes the neuro-immune status in depression and depression-like behaviours. As such, during physical activity increases are noted for, IL-10, IL-6 (transiently), macrophage migration inhibitory factor, central nervous system-specific auto-reactive CD4+ T cells, M2 microglia, astrocytes, CX3CL1 and insulin-growth factor-1 [99], all of which may have beneficial neuro-immunological effects in the management of depression. However, detrimental decreases are noted for the Th1/Th2 balance, pro-inflammatory cytokines, CRP, M1 microglia and reactive astrocytes [99]. Furthermore, swimming exercise decreases depression-like behaviour by decreasing serum corticosterone, IFN-gamma, TNF-alpha, indoleamine-2,3-deoxygenase (IDO) and increasing 5-HT levels [100]. Thus, swimming may inhibit the activation of inflammation and IDO pathways induced by stress, resulting in improved depressive states. Further investigation is warranted on the neuro-immune effects during exercise in depression. In addition, the effects of T regulatory cells, CD4+ T cells, CD8+ T cells, CD200, chemokines, macrophages, monocytes, dendritic cells, TNF-alpha and other cytokines during exercise in patients with depression, would result in useful information in the use of exercise and its manipulation, in the treatment of depression.

An important question with regard to physical activity, immunological factors and mental health is that of causality. Prospective epidemiological evidence suggests that depression is associated with low levels of physical activity and reduced cardiorespiratory fitness. In addition, physical inactivity is a predictor of sustained depression. That is, low physical activity levels precede the response to depression whereas individuals who maintain physically active are less likely to develop depression [101]. However, the role of the immune system in this needs further research. Hence, it is unclear what the protective factors to decreased mental health are in physically active and inactive individuals.

#### **f. Autoimmunity**

The incidence of autoimmune diseases has increased 3-fold in the last few decades. This includes diseases such as, lupus, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, Sjogren's syndrome, fibromyalgia, psoriasis and hypothyroidism. Autoimmunity is a condition where the body's immune system destroys itself causing chronic systemic inflammation and subsequent tissue destruction. For example, in multiple sclerosis high levels of IFN-gamma, TNF-alpha and IL-17 are present, whilst, the anti-inflammatory cytokines IL-6 and IL-10 are associated with remission periods of the disease [102]. In a combined (stretch, aerobic, resistance) exercise program in multiple sclerosis patients for 8 weeks, resulted in increased muscle strength and balance, and decrease in IL-17 and IFN-gamma levels [103]. Furthermore, people presenting with an autoimmune disorder are commonly faced with issues of muscle weakness, fatigue, and painful joints. However, with a structured exercise training regime, one does not only increase physical fitness but also quality of life. Indeed, in a 12 week resistance training program, in 42 multiple sclerosis (MS) patients, improved

voluntary isometric contraction and muscle power were noted in those undergoing the training program as compared to those who did not [104]. Further, improvements to physical and psychological functioning, fatigue and quality of life are noted [105, 106], in addition to, improved ambulatory function and mood status [107], in MS patients taking part in exercise activity. A 2 year blind, parallel-group, randomized controlled trial is currently being assessed in 240 multiple sclerosis patients, to determine the effects of exercise to reduce disability and to promote health [108].

In rheumatoid arthritis, excess levels (up to 100 times excess) of TNF-alpha, IL-6, IL-1beta, CRP and leukotriene B4 are known to contribute to the inflammatory state that ultimately destroys joint cartilage and synovial fluid. In addition, rheumatoid arthritis patients have an increased CVD risk factor profile, accounting for nearly 40% of their mortality, and a 2-fold increase in myocardial infarction and stroke, which may be attributed to being less physically active with poor aerobic fitness. Indeed, physically inactive rheumatoid arthritis patients have higher systolic blood pressure and elevated total cholesterol and LDL levels, as compared to physically active rheumatoid arthritis patients [109]. In addition, the chronic state of inflammation in rheumatoid arthritis patients enhances the development of atherosclerosis and may be a contributing factor for the increased CVD risk. Importantly, many patients don't participate in exercise programs, as they do not feel safe, and there are no 'specialist' programs tailored to such patients, hence, such programs should be included in studies. The benefits of exercise in autoimmune diseases and the subsequent immunological changes and their role in disease management requires further research, and a clearer understanding is necessary for the inclusion of exercise as a prescription in their treatment and management program.

#### **g. Cancer**

The cancer council Victoria, Australia, recommends up to one hour moderate or 30 minutes of vigorous physical activity daily to reduce the risk of cancer [110]. Sedentary lifestyle is responsible for at least one-third of deaths due to colon and other cancers [111]. Indeed, in a case control study with 1,130 breast cancer patients and 1,142 control subjects demonstrated a significant decreased risk of breast cancer in women with lower body mass index and those that were involved in regular physical activity [112]. Thirty to 60 minutes per day of physical activity reduces the risk of colon cancer by 30-40% in a dose response relationship, and breast cancer risk is decreased by 25-30% in physically active women compared to inactive women. It is clear that exercise may help prevent the development of certain cancers, notably colon and breast cancers, with prostate cancer having inconclusive evidence, lung cancer only having a few studies published, and there is little information on the role of exercise in preventing other cancers [113]. Interestingly, a review assessing the relationship between physical activity and risk of gastric cancer, in 1,535,006 people with 7,944 cases of gastric cancer, noted a protective association between physical activity and gastric cancer risk. The association was influenced in smokers, however the association was not influenced by alcohol, total energy intake, consumption of vegetables and fruits and infection with *Helicobacter pylori* [114].

Furthermore, exercise has also been shown to improve a number of cancer related factors in patients with cancer. Exercise improves quality of life, reduces side effects from peripheral neuropathy, improves balance control and physical performance in a study comprising 61 lymphoma patients [115]. Likewise, in breast and prostate cancer patients, daily walking or an exercise program reduces fatigue, improves symptoms and

quality of life during adjuvant chemotherapy [116, 117]. In addition, engaging in physical activity reduces the risk of breast cancer recurrence [118]. The effect of exercise on immune function in patients with cancer however, is limited and additional research is required to understand the mechanism involved in exercise and immune function and its link to clinical outcome. Understanding the changes to neutrophils, natural killer cells, T cells, monocytes and cytokines during exercise in cancer patients, will result in an exercise immunotherapeutic approach for treating the disease. Indeed, the ProImmune study is the first trial investigating the effects of 6 months of endurance exercise training in prostate cancer patients, and determining the effects to immune parameters, IL-6, MIF, IGF-1, testosterone, immune cell ratios, oxidative stress, as well as VO<sub>2</sub> peak, fatigue and quality of life [119]. Interestingly, elderly subjects (70-77 years old) subjected to an exercise program for 12 weeks, demonstrated significant decrease in carcinoembryonic antigen, an antigen over expressed on adenocarcinoma cells, which may contribute to preventing cancer in the elderly.

#### **h. Alzheimer's disease**

Vascular disease is associated with increased risk of Alzheimer disease, and habitual aerobic exercises has been shown to improve disease outcomes [120]. Acute aerobic exercise in adults with Alzheimer disease is associated with increase brain-derived neurotrophic factor levels which may contribute to decreased cognitive impairment in Alzheimer disease [121]. Likewise, long term treadmill exercise inhibits the progression of Alzheimer disease, by reduction of beta-amyloid deposition and tau phosphorylation in the hippocampus and inhibition of GSK3 [122]. In a randomised controlled trial of 210 Alzheimer disease patients, those that were involved in an exercise program resulted in longer physical functioning without causing any adverse effects [123].

#### **i. Conclusion**

It is clear that short term and long term exercise alters the number and function of immune cells. However, the exact role of these changes and their role in susceptibility to disease and outcome, is not clear [26]. Whether the increase in immune cells is a good thing or a bad thing, is still not well understood. In addition, studies have reported that TLR-4 expression on antigen presenting cells is temporarily reduced following exercise which leaves an 'open window' for upper respiratory tract infections and post-exercise immune-suppression. Further research is required to understand the role exercise plays on immune cells and their relationship to altering disease outcomes. It is also not clear, how exercise duration, frequency and intensity might influence immune parameters. Furthermore, high-intensity interval training (HIT) has sparked interest in people who cannot exercise for long. Hence, lack of time has been one of the main reasons people do not engage in regular physical activity. Benefits of HIT have been shown in weight loss, improving athletic performance and physical fitness, and improving numerous diseases (including type-2 diabetes and cardiometabolic disorders) [124-126]. More needs to be known about the effects of immune functioning on HIT training, strength training and other exercises.

#### **Expert Opinion and Five year view**

A plethora of evidence is available indicating that low levels of physical activity, low levels of cardiorespiratory fitness and high levels of sedentary behaviors are linked with higher risk of CHD and CVD, type-2 diabetes, psychological factors, allergies, cancer, autoimmunity and metabolic syndrome. It is important however, to consider other factors that may counteract or enhance the effects of regular exercise to disease outcome. Such factors, include, the use of herbs, probiotics, supplements (vitamins and minerals), diet (high in fruits, vegetables, whole grains, anti-inflammatory foods), keeping a healthy weight, smoking, alcohol consumption, adequate sleep and radiation exposure (eg. hours of mobile phone and computer use). Understanding the changes and functionality of all immune cells at the cellular and molecular level, could lead to novel exercise-immune-based therapies for the treatment of disease progression or prevention. In the next 5-years, much research is required to understand the immunological reactions during short and long term exercise, including aerobic, strength and HIT exercise, and how this information could be used to manipulate the immune system through exercise as a novel immunotherapeutic regime to treat disease.

### **Key issues**

- Physical activity keeps the metabolic balance, improves cardiovascular health, and influences autoimmune disease outcomes.
- Physical activity improves physiological and psychological outcomes of most patients
- Exercise aids in preventing cancer, and, improves recurrence rates and quality of life in cancer patients.
- Exercise decreases inflammation such as, CRP, TNF-alpha, L-6, IL-1beta, TLR2, TLR4, CD36, MHC-class II, although in some exercise regimes IL-6 is upregulated in the circulation and by muscle cells.

### **Acknowledgements**

*Dr Erika Borkoles' work is supported through the Australian Government's Collaborative Research Networks (CRN) program.*

### **Financial & competing interests disclosure**

*The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.*

### **References**

Papers of special note have been highlighted as:

- of interest
  - of considerable interest
1. Vichealth: Encouraging regular physical activity.  
<http://www.vichealth.vic.gov.au/Programs-and-Projects/Physical-Activity/PA-Overview.aspx>, Retrieved 5 May (2014).

2. Lafontaine TP, Dilorenzo TM, Frensch PA, Stucky-Ropp RC, Bargman EP, McDonald DG: Aerobic exercise and mood. A brief review, 1985-1990. *Sports medicine* 13(3), 160-170 (1992).
3. Lavie CJ, Milani RV, Artham SM, Gilliland Y: Psychological factors and cardiac risk and impact of exercise training programs-a review of ochsner studies. *The Ochsner journal* 7(4), 167-172 (2007).
  - A nice review of the effects of exercise on psychological factors in patients
4. Meng X, D'arcy C: The projected effect of increasing physical activity on reducing the prevalence of common mental disorders among Canadian men and women: a national population-based community study. *Preventive medicine* 56(1), 59-63 (2013).
5. Stojanovska L, Apostolopoulos V, Polman R, Borkoles E: To exercise, or, not to exercise, during menopause and beyond. *Maturitas* 77(4), 318-323 (2014).
  - A nice review of the effects of exercise in alleviating symptoms of menopause
6. De Souza Santos CA, Dantas EE, Moreira MH: Correlation of physical aptitude; functional capacity, corporal balance and quality of life (QoL) among elderly women submitted to a post-menopausal physical activities program. *Archives of gerontology and geriatrics* 53(3), 344-349 (2011).
7. (Who) WHO: New physical activity guidance can help reduce risk of breast, colon cancers. [http://www.who.int/mediacentre/news/notes/2011/world\\_cancer\\_day\\_20110204/en/index.html?utm\\_source=twitterfeed&utm\\_medium=twitter](http://www.who.int/mediacentre/news/notes/2011/world_cancer_day_20110204/en/index.html?utm_source=twitterfeed&utm_medium=twitter), (2011).
8. Australian Government DOH: Australia's Physical activity and sedentary behaviour guidelines. Fact sheet: 18-64 years. <http://health.gov.au/internet/main/publishing.nsf/Content/phy-activity>, (2014).
9. Porter D: Calculating health and social change: an essay on Jerry Morris and Late-modernist epidemiology. *International journal of epidemiology* 36(6), 1180-1184 (2007).
10. Kuper S: The man who invented exercise. *Financial Times*. , (2009. Retrieved 12 September 2009.).
11. Morris J, Heady J, Raffle P, Roberts C, Jw P: Coronary heart-disease and physical activity of work. *Lancet* 265(6795), 1053-1057 (1953).
  - One of the earliest studies demonstrating that physical activity has positive effects to cardiovascular disease outcomes
12. Morris J, Crawford M: Coronary Heart Disease and Physical Activity of Work. *BMJ* 2(5111), 1485-1496 (1958).
13. Fatone C, Guescini M, Balducci S *et al.*: Two weekly sessions of combined aerobic and resistance exercise are sufficient to provide beneficial effects in subjects with Type 2 diabetes mellitus and metabolic syndrome. *Journal of endocrinological investigation* 33(7), 489-495 (2010).
14. Grau AJ, Barth C, Geletneky B *et al.*: Association between recent sports activity, sports activity in young adulthood, and stroke. *Stroke; a journal of cerebral circulation* 40(2), 426-431 (2009).
15. Katzmarzyk PT: Physical activity, sedentary behavior, and health: paradigm paralysis or paradigm shift? *Diabetes* 59(11), 2717-2725 (2010).
16. Katzmarzyk PT, Church TS, Craig CL, Bouchard C: Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Medicine and science in sports and exercise* 41(5), 998-1005 (2009).
  - The correlation of the duration of sitting time to disease outcomes
17. Ainsworth BE, Sternfeld B, Slattery ML, Daguiuse V, Zahm SH: Physical activity and breast cancer: evaluation of physical activity assessment methods. *Cancer* 83(3 Suppl), 611-620 (1998).
18. Chlebowski RT: Nutrition and physical activity influence on breast cancer incidence and outcome. *Breast* 22 Suppl 2, S30-37 (2013).
19. Eriksen W, Bruusgaard D: Do physical leisure time activities prevent fatigue? A 15 month prospective study of nurses' aides. *British journal of sports medicine* 38(3), 331-336 (2004).

20. McMurray RG, Ainsworth BE, Harrell JS, Griggs TR, Williams OD: Is physical activity or aerobic power more influential on reducing cardiovascular disease risk factors? *Medicine and science in sports and exercise* 30(10), 1521-1529 (1998).
21. Eguchi E, Iso H, Tanabe N, Yatsuya H, Tamakoshi A, On Behalf of the Japan Collaborative Cohort Study G: Is the Association between Healthy Lifestyle Behaviors and Cardiovascular Mortality Modified by Overweight Status? The Japan Collaborative Cohort Study. *Preventive medicine*, (2014).
22. Jia LL, Kang YM, Wang FX *et al.*: Exercise training attenuates hypertension and cardiac hypertrophy by modulating neurotransmitters and cytokines in hypothalamic paraventricular nucleus. *PloS one* 9(1), e85481 (2014).
23. Park YM, Myers M, Vieira-Potter VJ: Adipose tissue inflammation and metabolic dysfunction: role of exercise. *Missouri medicine* 111(1), 65-72 (2014).
24. Radom-Aizik S, Zaldivar FP, Jr., Haddad F, Cooper DM: Impact of brief exercise on circulating monocyte gene and microRNA expression: Implications for atherosclerotic vascular disease. *Brain, behavior, and immunity*, (2014).
- Immunological changes of benefit to cardiovascular health
25. Okutsu M, Suzuki K, Ishijima T, Peake J, Higuchi M: The effects of acute exercise-induced cortisol on CCR2 expression on human monocytes. *Brain, behavior, and immunity* 22(7), 1066-1071 (2008).
26. Walsh NP, Gleeson M, Shephard RJ *et al.*: Position statement. Part one: Immune function and exercise. *Exercise immunology review* 17, 6-63 (2011).
- The changes of immune cells after exercise
27. Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM: Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *Journal of applied physiology* 114(5), 628-636 (2013).
28. Zaldivar F, Wang-Rodriguez J, Nemet D *et al.*: Constitutive pro- and anti-inflammatory cytokine and growth factor response to exercise in leukocytes. *Journal of applied physiology* 100(4), 1124-1133 (2006).
29. Simpson RJ, Cosgrove C, Ingram LA *et al.*: Senescent T-lymphocytes are mobilised into the peripheral blood compartment in young and older humans after exhaustive exercise. *Brain, behavior, and immunity* 22(4), 544-551 (2008).
30. Simpson RJ, Florida-James GD, Cosgrove C *et al.*: High-intensity exercise elicits the mobilization of senescent T lymphocytes into the peripheral blood compartment in human subjects. *Journal of applied physiology* 103(1), 396-401 (2007).
31. Simpson RJ, Mcfarlin BK, Mcsporrnan C, Spielmann G, O Hartaigh B, Guy K: Toll-like receptor expression on classic and pro-inflammatory blood monocytes after acute exercise in humans. *Brain, behavior, and immunity* 23(2), 232-239 (2009).
32. Hong S, Mills PJ: Effects of an exercise challenge on mobilization and surface marker expression of monocyte subsets in individuals with normal vs. elevated blood pressure. *Brain, behavior, and immunity* 22(4), 590-599 (2008).
33. Radom-Aizik S, Zaldivar F, Jr., Leu SY, Galassetti P, Cooper DM: Effects of 30 min of aerobic exercise on gene expression in human neutrophils. *Journal of applied physiology* 104(1), 236-243 (2008).
34. Garcia JJ, Bote E, Hinchado MD, Ortega E: A single session of intense exercise improves the inflammatory response in healthy sedentary women. *Journal of physiology and biochemistry* 67(1), 87-94 (2011).
- Inflammatory changes after a single bout of exercise. The importance of exercise and the inflammatory milieu
35. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA: The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature reviews. Immunology* 11(9), 607-615 (2011).
- An excellent review on the mechanisms of exercise and its effects on inflammation
36. Pinto A, Di Raimondo D, Tuttolomondo A, Butta C, Milio G, Licata G: Effects of physical exercise on inflammatory markers of atherosclerosis. *Current pharmaceutical design* 18(28), 4326-4349 (2012).

37. Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD: Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? *Journal of leukocyte biology* 84(5), 1271-1278 (2008).
- Decrease in CD14+CD16+ blood monocyte levels after exercise
38. Phillips MD, Flynn MG, Mcfarlin BK, Stewart LK, Timmerman KL: Resistance training at eight-repetition maximum reduces the inflammatory milieu in elderly women. *Medicine and science in sports and exercise* 42(2), 314-325 (2010).
39. Huang CJ, Zourdos MC, Jo E, Ormsbee MJ: Influence of physical activity and nutrition on obesity-related immune function. *TheScientificWorldJournal* 2013, 752071 (2013).
40. Coen PM, Flynn MG, Markofski MM, Pence BD, Hannemann RE: Adding exercise to rosuvastatin treatment: influence on C-reactive protein, monocyte toll-like receptor 4 expression, and inflammatory monocyte (CD14+CD16+) population. *Metabolism: clinical and experimental* 59(12), 1775-1783 (2010).
41. Bishop NC, Hayashida H, Clark M, Coombs C, Miller S, Stensel DJ: Effect of acute and regular exercise on growth hormone secretagogue receptor-1a expression in human lymphocytes, T cell subpopulation and monocytes. *Brain, behavior, and immunity*, (2013).
42. Asghar M, George L, Lokhandwala MF: Exercise decreases oxidative stress and inflammation and restores renal dopamine D1 receptor function in old rats. *American journal of physiology. Renal physiology* 293(3), F914-919 (2007).
43. Dugger KJ, Chrisman T, Jones B *et al.*: Moderate aerobic exercise alters migration patterns of antigen specific T helper cells within an asthmatic lung. *Brain, behavior, and immunity* 34, 67-78 (2013).
- Alterations of immune cell migration following exercise
44. Woods JA, Vieira VJ, Keylock KT: Exercise, inflammation, and innate immunity. *Immunology and allergy clinics of North America* 29(2), 381-393 (2009).
45. Cook MD, Martin SA, Williams C *et al.*: Forced treadmill exercise training exacerbates inflammation and causes mortality while voluntary wheel training is protective in a mouse model of colitis. *Brain, behavior, and immunity* 33, 46-56 (2013).
46. Hoffman-Goetz L, Pervaiz N, Packer N, Guan J: Freewheel training decreases pro- and increases anti-inflammatory cytokine expression in mouse intestinal lymphocytes. *Brain, behavior, and immunity* 24(7), 1105-1115 (2010).
47. Yano H, Uchida M, Nakai R *et al.*: Exhaustive exercise reduces TNF-alpha and IFN-alpha production in response to R-848 via toll-like receptor 7 in mice. *European journal of applied physiology* 110(4), 797-803 (2010).
48. Kawanishi N, Yano H, Mizokami T, Takahashi M, Oyanagi E, Suzuki K: Exercise training attenuates hepatic inflammation, fibrosis and macrophage infiltration during diet induced-obesity in mice. *Brain, behavior, and immunity* 26(6), 931-941 (2012).
49. Szostak J, Laurant P: The forgotten face of regular physical exercise: a 'natural' anti-atherogenic activity. *Clinical science* 121(3), 91-106 (2011).
50. Touati S, Meziri F, Devaux S, Berthelot A, Touyz RM, Laurant P: Exercise reverses metabolic syndrome in high-fat diet-induced obese rats. *Medicine and science in sports and exercise* 43(3), 398-407 (2011).
51. Bassett DR, Schneider PL, Huntington GE: Physical activity in an Old Order Amish community. *Medicine and science in sports and exercise* 36(1), 79-85 (2004).
52. Lipman RL, Raskin P, Love T, Triebwasser J, Lecocq FR, Schnure JJ: Glucose intolerance during decreased physical activity in man. *Diabetes* 21(2), 101-107 (1972).
53. Di Pietro L, Dziura J, Blair SN: Estimated change in physical activity level (PAL) and prediction of 5-year weight change in men: the Aerobics Center Longitudinal Study. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity* 28(12), 1541-1547 (2004).
54. Thompson PD, Buchner D, Pina IL *et al.*: Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation* 107(24), 3109-3116 (2003).

55. Seo DI, So WY, Ha S *et al.*: Effects of 12 weeks of combined exercise training on visfatin and metabolic syndrome factors in obese middle-aged women. *Journal of sports science & medicine* 10(1), 222-226 (2011).
56. Stevenson ET, Davy KP, Jones PP, Desouza CA, Seals DR: Blood pressure risks factors in healthy postmenopausal women: physical activity and hormone replacement. *Journal of applied physiology* 82(2), 652-660 (1997).
57. Gelecek N, Ilcin N, Subasi SS, Acar S, Demir N, Ormen M: The effects of resistance training on cardiovascular disease risk factors in postmenopausal women: a randomized-controlled trial. *Health care for women international* 33(12), 1072-1085 (2012).
58. Earnest CP, Johannsen NM, Swift DL, Lavie CJ, Blair SN, Church TS: Dose effect of cardiorespiratory exercise on metabolic syndrome in postmenopausal women. *The American journal of cardiology* 111(12), 1805-1811 (2013).
59. Hong S, Dimitrov S, Pruitt C, Shaikh F, Beg N: Benefit of physical fitness against inflammation in obesity: Role of beta adrenergic receptors. *Brain, behavior, and immunity*, (2013).
60. Hunter SD, Dhindsa M, Cunningham E, Tarumi T, Alkatan M, Tanaka H: Improvements in glucose tolerance with Bikram yoga in older obese adults: a pilot study. *Journal of bodywork and movement therapies* 17(4), 404-407 (2013).
61. Hunter SD, Dhindsa MS, Cunningham E *et al.*: The effect of Bikram yoga on arterial stiffness in young and older adults. *Journal of alternative and complementary medicine* 19(12), 930-934 (2013).
62. Agil A, Abike F, Daskapan A, Alaca R, Tuzun H: Short-term exercise approaches on menopausal symptoms, psychological health, and quality of life in postmenopausal women. *Obstetrics and gynecology international* 2010, (2010).
63. Bowles HR, Fitzgerald SJ, Morrow JR, Jr., Jackson AW, Blair SN: Construct validity of self-reported historical physical activity. *American journal of epidemiology* 160(3), 279-286 (2004).
64. Roberts CK, Won D, Pruthi S *et al.*: Effect of a short-term diet and exercise intervention on oxidative stress, inflammation, MMP-9, and monocyte chemotactic activity in men with metabolic syndrome factors. *Journal of applied physiology* 100(5), 1657-1665 (2006).
65. Roberts CK, Won D, Pruthi S, Lin SS, Barnard RJ: Effect of a diet and exercise intervention on oxidative stress, inflammation and monocyte adhesion in diabetic men. *Diabetes research and clinical practice* 73(3), 249-259 (2006).
66. Speaker KJ, Cox SS, Paton MM *et al.*: Six weeks of voluntary wheel running modulates inflammatory protein (MCP-1, IL-6, and IL-10) and DAMP (Hsp72) responses to acute stress in white adipose tissue of lean rats. *Brain, behavior, and immunity*, (2013).
- Voluntary habitual exercise augments the innate immune system, through increases in stress-evoked heat shock protein 72 (Hsp72), MCP-1, IL-6 and IL-10 and decreases inflammatory cytokines IL-1 beta and TNF-alpha.
67. Thompson D, Walhin JP, Batterham AM, Stokes KA, Cooper AR, Andrews RC: Effect of Diet or Diet Plus Physical Activity Versus Usual Care on Inflammatory Markers in Patients with Newly Diagnosed Type 2 Diabetes: The Early ACTivity In Diabetes (ACTID) Randomized, Controlled Trial. *Journal of the American Heart Association* 3(3), e000828 (2014).
- Soluble intercellular adhesion molecule-1 (sICAM-1) levels are significantly improved in physically active type-2 diabetic patients.
68. Thomas AW, Davies NA, Moir H *et al.*: Exercise-associated generation of PPARgamma ligands activates PPARgamma signaling events and upregulates genes related to lipid metabolism. *Journal of applied physiology* 112(5), 806-815 (2012).
- Exercise up-regulates peroxisome proliferator-activated receptor-gamma (PPAR-gamma) in the plasma and on monocytes.
69. Pedersen BK: Exercise-induced myokines and their role in chronic diseases. *Brain, behavior, and immunity* 25(5), 811-816 (2011).
- Myokines, such as IL-6 are released by muscle cells during exercise, which have anti-inflammatory effects.



70. Bartfay W, Bartfay E: A case-control study examining the effects of active versus sedentary lifestyles on measures of body iron burden and oxidative stress in postmenopausal women. *Biological research for nursing* 16(1), 38-45 (2014).
71. Lamonte MJ, Nichaman MZ, Blair SN: Physical activity and the metabolic syndrome association with myocardial infarction and stroke. *Circulation* 109(22), e314; author reply e314 (2004).
72. Ninomiya JK, L'italien G, Criqui MH, Whyte JL, Gamst A, Chen RS: Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. *Circulation* 109(1), 42-46 (2004).
73. Nocon M, Hiemann T, Muller-Riemenschneider F, Thala F, Roll S, Willich SN: Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 15(3), 239-246 (2008).
74. Fletcher GF, Blair SN, Blumenthal J *et al.*: Statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart association. *Circulation* 86(1), 340-344 (1992).
75. Services UDOHaH: Physical Activity and Health: A Report of the Surgeon General. Atlanta, Ga. *US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Disease Control and Prevention and Health Promotion*, (1996).
76. Services UDOHaH: Physical Activity Guidelines for Americans. <http://www.health.gov/paguidelines/>. Accessed January 5, 2014. , (2008).
77. Shiroma E, Lee I-M: Exercise in Cardiovascular Disease. Physical Activity and Cardiovascular Health. Lessons Learned From Epidemiological Studies Across Age, Gender, and Race/Ethnicity. *Circulation* 122, 743-752 (2010).
78. Franklin BA, Lavie CJ: Triggers of acute cardiovascular events and potential preventive strategies: prophylactic role of regular exercise. *The Physician and sportsmedicine* 39(4), 11-21 (2011).
79. Hambrecht R, Wolf A, Gielen S *et al.*: Effect of exercise on coronary endothelial function in patients with coronary artery disease. *The New England journal of medicine* 342(7), 454-460 (2000).
80. Hambrecht R, Gielen S, Linke A *et al.*: Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *JAMA : the journal of the American Medical Association* 283(23), 3095-3101 (2000).
81. Kwasniewska M, Jegier A, Kostka T *et al.*: Long-term effect of different physical activity levels on subclinical atherosclerosis in middle-aged men: a 25-year prospective study. *PloS one* 9(1), e85209 (2014).
82. Peschel T, Sixt S, Beitz F *et al.*: High, but not moderate frequency and duration of exercise training induces downregulation of the expression of inflammatory and atherogenic adhesion molecules. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 14(3), 476-482 (2007).
83. Wang JS, Chen YW, Chow SE, Ou HC, Sheu WH: Exercise paradoxically modulates oxidized low density lipoprotein-induced adhesion molecules expression and trans-endothelial migration of monocyte in men. *Thrombosis and haemostasis* 94(4), 846-852 (2005).
84. Kohut ML, Mccann DA, Russell DW *et al.*: Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain, behavior, and immunity* 20(3), 201-209 (2006).
- Demonstration that aerobic exercise, but not resistance exercise, reduces CRP, IL-18 and IL-6, all markers of inflammation which are mediators associated with numerous diseases including atherosclerosis and hypertension

85. Lavie CJ, Church TS, Milani RV, Earnest CP: Impact of physical activity, cardiorespiratory fitness, and exercise training on markers of inflammation. *Journal of cardiopulmonary rehabilitation and prevention* 31(3), 137-145 (2011).
86. Hambrecht R, Niebauer J, Marburger C *et al.*: Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *Journal of the American College of Cardiology* 22(2), 468-477 (1993).
87. Fearon IM, Faux SP: Oxidative stress and cardiovascular disease: novel tools give (free) radical insight. *Journal of molecular and cellular cardiology* 47(3), 372-381 (2009).
88. Baraas F, Rilantono L, Diniharini S, Kurniawan I, Christian R, Kusmana D: Effect of short-term low-intensity exercise training on association of oxygen free radicals and nitric oxide production in patients with acute myocardial infarction. *The International journal of angiology : official publication of the International College of Angiology, Inc* 22(3), 159-164 (2013).
89. Piotrowicz R, Wolszakiewicz J: Cardiac rehabilitation following myocardial infarction. *Cardiology journal* 15(5), 481-487 (2008).
90. Wang JS, Lee T, Chow SE: Role of exercise intensities in oxidized low-density lipoprotein-mediated redox status of monocyte in men. *Journal of applied physiology* 101(3), 740-744 (2006).
91. Blair SN, Church TS: The fitness, obesity, and health equation: is physical activity the common denominator? *JAMA : the journal of the American Medical Association* 292(10), 1232-1234 (2004).
92. Iellamo F, Caminiti G, Sposato B *et al.*: Effect of High-Intensity interval training versus moderate continuous training on 24-h blood pressure profile and insulin resistance in patients with chronic heart failure. *Internal and emergency medicine*, (2013).
93. Lavie CJ, Milani RV, O'keefe JH, Lavie TJ: Impact of exercise training on psychological risk factors. *Progress in cardiovascular diseases* 53(6), 464-470 (2011).
94. North TC, Mccullagh P, Tran ZV: Effect of exercise on depression. *Exercise and sport sciences reviews* 18, 379-415 (1990).
95. Mckercher C, Patton GC, Schmidt MD, Venn AJ, Dwyer T, Sanderson K: Physical activity and depression symptom profiles in young men and women with major depression. *Psychosomatic medicine* 75(4), 366-374 (2013).
96. Hatta A, Nishihira Y, Higashiura T: Effects of a single bout of walking on psychophysiological responses and executive function in elderly adults: a pilot study. *Clinical interventions in aging* 8, 945-952 (2013).
97. Guskowska M, Langwald M, Dudziak D, Zaremba A: Influence of a single physical exercise class on mood states of pregnant women. *Journal of psychosomatic obstetrics and gynaecology* 34(2), 98-104 (2013).
98. Polman R, Kaiseler M, Borkoles E: Effect of a single bout of exercise on the mood of pregnant women. *The Journal of sports medicine and physical fitness* 47(1), 103-111 (2007).
99. Eyre HA, Papps E, Baune BT: Treating depression and depression-like behavior with physical activity: an immune perspective. *Frontiers in psychiatry* 4, 3 (2013).
100. Liu W, Sheng H, Xu Y, Liu Y, Lu J, Ni X: Swimming exercise ameliorates depression-like behavior in chronically stressed rats: relevant to proinflammatory cytokines andIDO activation. *Behavioural brain research* 242, 110-116 (2013).
101. Mutrie N: The Relationship between Physical Activity and Clinically Defined Depression. In S.J.H. Biddle, K.R Fox, & S.H. Boutcher (editors), *Physical Activity and Psychological Well-Being*. London, UK: Routledge, 46-62 (2000).
102. Florindo M: Inflammatory Cytokines and Physical Activity in Multiple Sclerosis. *ISRN neurology* 2014, 151572 (2014).
103. Golzari Z, Shabkhiz F, Soudi S, Kordi MR, Hashemi SM: Combined exercise training reduces IFN-gamma and IL-17 levels in the plasma and the supernatant of peripheral blood mononuclear cells in women with multiple sclerosis. *International immunopharmacology* 10(11), 1415-1419 (2010).

104. Medina-Perez C, De Souza-Teixeira F, Fernandez-Gonzalo R, De Paz-Fernandez JA: Effects of a resistance training program and subsequent detraining on muscle strength and muscle power in multiple sclerosis patients. *NeuroRehabilitation*, (2014).
105. Carter A, Daley A, Humphreys L *et al.*: Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial. *Multiple sclerosis*, (2014).
106. Tosh J, Dixon S, Carter A *et al.*: Cost effectiveness of a pragmatic exercise intervention (EXIMS) for people with multiple sclerosis: economic evaluation of a randomised controlled trial. *Multiple sclerosis*, (2014).
107. Ahmadi A, Arastoo AA, Nikbakht M, Zahednejad S, Rajabpour M: Comparison of the Effect of 8 weeks Aerobic and Yoga Training on Ambulatory Function, Fatigue and Mood Status in MS Patients. *Iranian Red Crescent medical journal* 15(6), 449-454 (2013).
108. Mayo NE, Bayley M, Duquette P, Lapierre Y, Anderson R, Bartlett S: The role of exercise in modifying outcomes for people with multiple sclerosis: a randomized trial. *BMC neurology* 13, 69 (2013).
109. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF *et al.*: Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology* 16(2), 188-194 (2009).
- A nice article demonstrating the association of physical inactivity with increased cardiovascular disease in patients with rheumatoid arthritis.
110. Cancer Council Victoria A: Be physically active. <http://www.cancervic.org.au/preventing-cancer/be-physically-active>, (2014, accessed 20 December 2014).
111. Booth FW, Gordon SE, Carlson CJ, Hamilton MT: Waging war on modern chronic diseases: primary prevention through exercise biology. *Journal of applied physiology* 88(2), 774-787 (2000).
112. Sangrajang S, Chaiwerawattana A, Ploysawang P, Nooklang K, Jamsri P, Somharnwong S: Obesity, diet and physical inactivity and risk of breast cancer in thai women. *Asian Pacific journal of cancer prevention : APJCP* 14(11), 7023-7027 (2013).
113. Lee IM: Physical activity and cancer prevention--data from epidemiologic studies. *Medicine and science in sports and exercise* 35(11), 1823-1827 (2003).
114. Abioye AI, Odesanya MO, Abioye AI, Ibrahim NA: Physical activity and risk of gastric cancer: a meta-analysis of observational studies. *British journal of sports medicine*, (2014).
115. Streckmann F, Kneis S, Leifert JA *et al.*: Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 25(2), 493-499 (2014).
116. Backman M, Wengstrom Y, Johansson B *et al.*: A randomized pilot study with daily walking during adjuvant chemotherapy for patients with breast and colorectal cancer. *Acta oncologica*, (2014).
117. Cormie P, Galvao DA, Spry N, Joseph D, Taaffe DR, Newton RU: Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: longitudinal results of a pilot study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer*, (2014).
118. Loprinzi PD, Cardinal BJ, Winters-Stone K, Smit E, Loprinzi CL: Physical activity and the risk of breast cancer recurrence: a literature review. *Oncology nursing forum* 39(3), 269-274 (2012).
119. Zimmer P, Jager E, Bloch W, Zopf EM, Baumann FT: Influence of a six month endurance exercise program on the immune function of prostate cancer patients undergoing Antiandrogen- or Chemotherapy: design and rationale of the Prolmmun study. *BMC cancer* 13(1), 272 (2013).
120. Tarumi T, Zhang R: Cerebral hemodynamics of the aging brain: risk of Alzheimer disease and benefit of aerobic exercise. *Frontiers in Physiology* 5, 6-13 (2014).

121. Coelho FG, Vital TM, Stein AM *et al.*: Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *Journal of Alzheimer's disease : JAD* 39(2), 401-408 (2014).
122. Liu HL, Zhao G, Zhang H, Shi LD: Long-term treadmill exercise inhibits the progression of Alzheimer's disease-like neuropathology in the hippocampus of APP/PS1 transgenic mice. *Behavioural brain research* 256, 261-272 (2013).
123. Pitkala KH, Poysti MM, Laakkonen ML *et al.*: Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. *JAMA internal medicine* 173(10), 894-901 (2013).
124. Babraj JA, Volvaard NB, Keast C, Guppy FM, Cottrell G, Timmons JA: Extremely short duration high intensity interval training substantially improves insulin action in young healthy males. *BMC endocrine disorders* 9, 3 (2009).
125. Buchan DS, Ollis S, Thomas NE, Baker JS: The influence of a high intensity physical activity intervention on a selection of health related outcomes: an ecological approach. *BMC public health* 10, 8 (2010).
126. Gibala MJ, Little JP, Macdonald MJ, Hawley JA: Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of physiology* 590(Pt 5), 1077-1084 (2012).