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Inactivity and obesity: consequences for macrophage-mediated inflammation and the development of cardiometabolic disease

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Obesity and dyslipidaemia are strongly associated with the development of cardiometabolic diseases including CVD, stroke, type 2 diabetes, insulin resistance and non-alcoholic fatty liver disease. While these conditions are preventable, they are leading causes of mortality globally. There is now overwhelming clinical and experimental evidence that these conditions are driven by chronic systemic inflammation, with a growing body of data suggesting that this can be regulated by increasing levels of physical activity and reducing sedentary time. In this review we address the role of macrophage-mediated inflammation on the development of cardiometabolic diseases in individuals with overweight and obesity and how reducing sedentary behaviour and increasing physical activity appears to lessen these pro-inflammatory processes, reducing the risk of developing cardiometabolic diseases. While loss of subcutaneous and visceral fat mass is important for reducing chronic systemic inflammation, the mediating effects of increasing physical activity levels and lowering sedentary time on the development of inflamed adipose tissue also occur independently of changes in adiposity. The message that weight loss is not necessary for the benefits of physical activity in lowering chronic inflammation and improving health should encourage those for whom losing weight is difficult. Additionally, while the health benefits of meeting the recommended physical activity guidelines are clear, simply moving more appears to lower chronic systemic inflammation. Reducing sitting time and increasing light physical activity may therefore provide an alternative, more approachable manner for some with overweight and obesity to become more active, reduce chronic inflammation and improve cardiometabolic health.

Key words: Obesity and overweight: CVD: Inflammation: Physical activity

Obesity and overweight are defined by the WHO as 'abnormal or excessive adiposity that may impair health'[1]. Age-standardised estimates for 2016 from the WHO Global Health Observatory indicate about 40 % of adults aged 18 years and over were overweight, and approximately 13 % were obese[1]. In the WHO European Region overweight and obesity have now reached epidemic proportions; in 2022 an estimated 59 % of adults and nearly one in three children are living with overweight or obesity[1].

Abbreviations: ATM, adipose tissue macrophage; CRP, C-reactive protein; MVPA, moderate-to-vigorous physical activity; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

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Obesity and dyslipidaemia are strongly associated with the development of cardiometabolic diseases; a group of common conditions including CVD, stroke, type 2 diabetes, insulin resistance and non-alcoholic fatty liver disease. While these conditions are preventable, they are leading causes of mortality globally[1]. There is now overwhelming clinical and experimental evidence that these conditions are driven by chronic systemic inflammation[2,3], characterised by an enduring low-level elevation of circulating inflammatory cytokines, particularly IL-6 and TNF-α and hepatic-derived acute phase proteins, such as C-reactive protein (CRP) and fibrinogen.

The accumulation of excess adipose tissue in people with obesity is associated with marked increases in both localised and systemic inflammation[4]. Adipose tissue is a major source of circulating pro-inflammatory cytokines, with visceral, rather than subcutaneous, adipose tissue contributing disproportionately[5–7]. Superficial subcutaneous adipose tissue (SAT) is relatively benign, whereas deep subcutaneous deposits and visceral adipose tissue (VAT) are associated with adverse metabolic and inflammatory profiles[8]. Consequently, although BMI is commonly used to classify overweight or obesity, evidence indicates abdominal obesity – measured by waist circumference – is a better predictor of VAT and subsequent cardiometabolic disease risk[8]. As such, adipose-derived inflammation can be considered a primary determinant of central obesity-associated disease development. As reviewed in detail later, macrophages present within adipose tissue are the main contributors to local adipose-related inflammation and systemic 'spill-over' leading to low level yet persistent elevations (enduring over months and years) in circulating inflammatory biomarkers. This gives rise to the terms 'chronic low-grade inflammation', and 'chronic systemic inflammation', which are often used interchangeably, as opposed to acute inflammation, which is the body's normal response to localised tissue injury or damage and usually resolves in hours or days[9].

It is important to highlight that these circulating pro-inflammatory cytokines are not simply indicators of the presence of local tissue inflammation, rather they also play active roles systemically, contributing to the dysfunction in other tissues, including the vasculature, gut, liver, kidneys[10] and brain[11] contributing to a heightened risk of cardiometabolic disease. For example, chronic systemic inflammation drives vascular remodelling and accumulation of macrophages, mast cells, T cells and other materials in the inner layer of vascular walls[12]. Elevations in circulating IL-6 and TNF-α induce oxidative stress, further contributing to endothelial dysfunction and vascular inflammation characterised by abnormal coagulation and vascular leakage[13]. Subsequent production of reactive oxygen species, upregulation of adhesion molecules (e.g. V-CAM and I-CAM)[14] and stimulation of inflammatory processes within the vessel wall over time can promote atherosclerotic lesion formation[15]. Elevations in pro-inflammatory cytokines also destabilise atherosclerotic plaques formed by promoting cell apoptosis and matrix degradation, in addition to reducing the fibrinolytic actions of endothelial cells[12].

The damaging effects of systemic inflammation are not however limited to the impact on the vasculature. IL-6 also promotes leucocyte recruitment from the circulation into larger (e.g. adipose, liver), in addition to smaller (e.g. atherosclerotic plaques), sites of inflammation by upregulating endothelial cell expression of adhesion molecules and chemokines[16,17]. For example, circulating lymphocytes can infiltrate the liver in people with obesity due to chemokine receptor-driven homing; this is associated with an increased risk of developing non-alcoholic fatty liver disease and progression to non-alcoholic hepatic steatosis[10]. Furthermore, cytokines are cell diffusible proteins that can directly infiltrate these tissues, impeding mitochondrial dynamics, promoting reactive oxygen species production and subsequent cell death, which further amplifies resident tissue and systemic inflammation[11]. Cytokines can also induce widespread insulin resistance by inhibiting insulin signalling, and impairing lipid and glucose metabolism in tissues such as the liver and skeletal muscle[18,19]. Collectively, damage to whole-body systems encourages recruitment of more immune cells to these tissues, thereby promoting a persistent cycle of chronic inflammation (Fig. 1). Given that adipose tissue comprises over half the body mass of some individuals with obesity, inflamed adipose tissue has huge implications for inflammation-driven cardiometabolic disease risk.

Central obesity and chronic inflammation

Disturbances in tissue metabolism and immunity can synergistically elevate the risk of cardiometabolic disease. Hormones, signalling proteins and lipids mediate communication between these two systems that function to regulate one another. Immunometabolic processes rely on changes in a host of intra- and extracellular metabolites, such as glucose, amino acids and fatty acids[20]. Therefore, chronic disturbances in metabolism can result in harmful changes to the immune system, in turn promoting chronic inflammation. These changes are observed in malnourished individuals with immunosuppression[21], as well as in people with obesity[22]. Given that adipose tissue acts as both an endocrine and immunological organ, its dysfunction is central in increasing the risk of cardiometabolic disease in people with obesity. In this review we focus specifically on the roles of monocytes and macrophages in the development of chronic inflammation in obesity within the context of inflammatory characteristics shown to be influenced by physical activity and thus discussed later in this review. More detailed examinations of the biology of adipose tissue inflammation in obesity are available for interested readers[23–25].

Macrophage accumulation in obese adipose tissue

Macrophage accumulation within adipose tissue is a cellular hallmark of obesity[23]. Human subjects are born with tissue-resident macrophages; in lean adipose tissue

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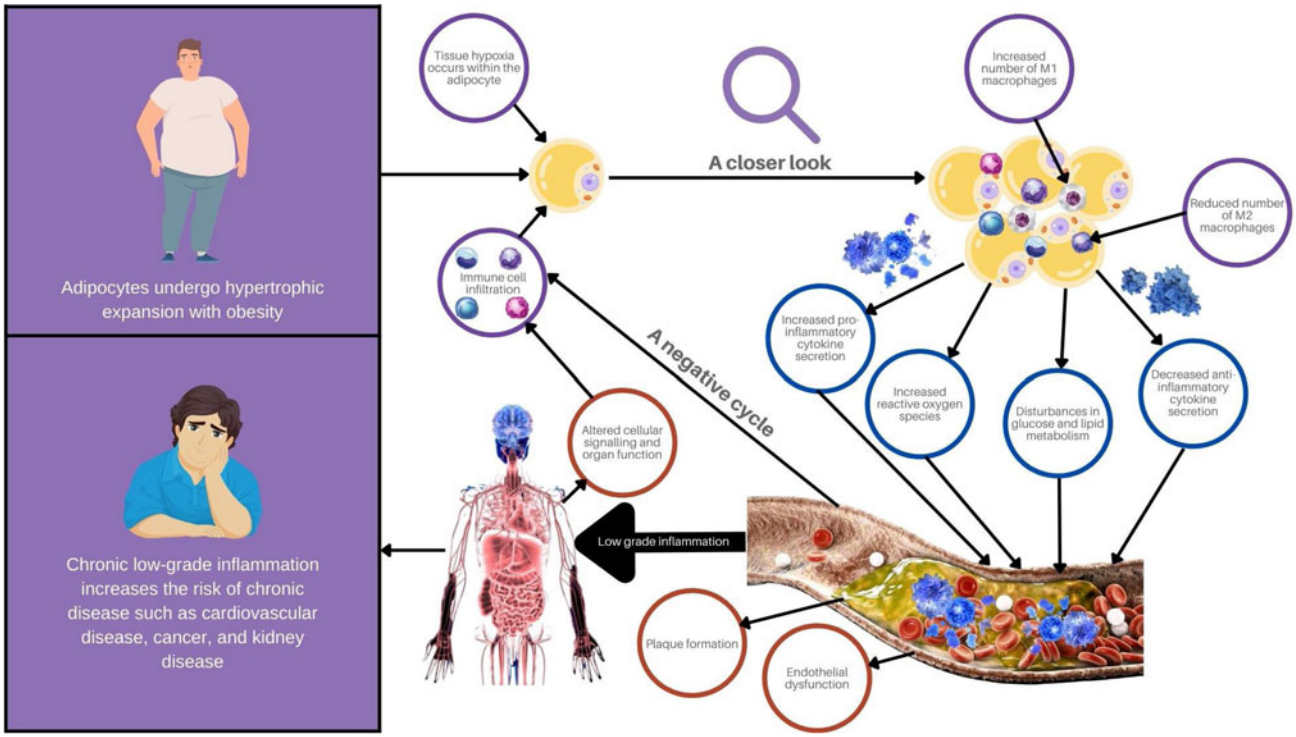

Fig. 1. Central obesity and chronic low-grade inflammation. Obesity is associated with the hypertrophy of adipocytes resulting in local tissue hypoxia. This results in increased immune cell infiltration of the adipose tissue and accumulation of pro-inflammatory macrophages (M1) along with a reduction in anti-inflammatory macrophages (M2) within the adipose tissue. Consequently, there is greater secretion of pro-inflammatory cytokines from adipose tissue and a reduction in anti-inflammatory cytokines, promoting the production of reactive oxygen species and disturbances in glucose and lipid metabolism. Given that adipose tissue comprises over half the body mass in some individuals with obesity, the local effects can spill over to whole-body systems through the circulation, underpinning vascular dysfunction, plaque formation and contributing to chronic low-grade inflammation which impacts cellular and organ function. This in turn increases the risk of chronic diseases, such as CVD, and encourages more immune cells to infiltrate tissues such as the liver, skeletal muscle and adipose tissue, thereby promoting a persistent cycle of chronic inflammation.

these are largely of the M2 phenotype that express high levels of arginase-1, which inhibits nitric oxide synthase activity, and secrete anti-inflammatory cytokines, such as IL-10 to help maintain cellular homoeostasis[26,27]. In contrast, obese human adipose tissue contains an abundance of M1 macrophages that secrete pro-inflammatory cytokines including IL-1β, IL-6, TNF-α and activate nitric oxide synthase, exacerbating the inflammatory processes that can be detrimental to health[28]. The dysregulated cytokine secretion and disruption to adipocyte signalling pathways associated with M1 macrophage overpopulation[29] can result in increased cytokine mRNA expression in the adipose tissue from people with obesity[30], insulin insensitivity, mitochondrial dysfunction and endoplasmic reticular stress[31]. Inflamed adipose tissue also contributes to chronic systemic inflammation by secreting adipokines, cytokines and lipids that impact the metabolism and health of peripheral tissues, as well as vascular function[31]. Given that adipose tissue comprises over half the body mass of some individuals with obesity, inflamed adipose tissue has a substantial involvement in inflammation-driven cardiometabolic disease risk.

In support, studies in rodents have shown that VAT is more heavily infiltrated with pro-inflammatory M1 macrophages than SAT[32] and adipose tissue from mice fed with a high-fat diet for 16 weeks demonstrated increased numbers of M1 macrophages (and CD8+ T cells), in addition to expressing higher levels of mRNA for TNF-α[33]. In human subjects, BMI was a significant predictor of transcript expression of the macrophage marker CD68 on abdominal SAT biopsies from individuals with BMI ranging from 19·4 to 60·1 kg/m^2 [27]. BMI and average adipocyte cross-sectional area were also strong predictors of the percentage of CD68-expressing adipose tissue macrophages (ATM)[27]. Similarly, abdominal SAT biopsies from thirty-nine non-diabetic adults across a range of BMI (20·5–45·8 kg/m^2) demonstrated that the number of ATM per 100 adipocytes increased with BMI, which was also positively and significantly correlated with total (CD68+), pro-inflammatory M1-type (CD14+) and anti-inflammatory M2-type (CD206+) macrophages[31]. Adipose tissue IL-6 was also significantly and positively associated with BMI[31], supporting the role of locally released IL-6 in the promotion of macrophage infiltration into adipose tissue[17]. The contribution of ATM numbers to systemic concentrations of chronic inflammatory markers was also evident; numbers of CD68 + ATM positively associated with circulating TNF-α and CRP,

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which in turn were associated with insulin sensitivity and skeletal muscle mitochondrial oxidative capacity[31]. This may be related to higher adipose IL-6 concentrations in obesity as this is associated with an inhibition in the synthesis and secretion of adiponectin – an insulin-sensitising and anti-inflammatory protein – exacerbating the pro-inflammatory microenvironment in adipose tissue[34]. More recently, a distinct pro-inflammatory macrophage phenotype has been discovered in obese adipose tissue that does not express the specific markers associated with M1 and M2 phenotypes, but rather markers associated with a state of metabolic activation, induced by high levels of NEFA, insulin and glucose[23].

Monocytes and obesity

Although in the early stages of obesity there is some proliferation of tissue-resident macrophages in response to local pro-inflammatory stimuli, macrophage recruitment from bone-marrow-derived blood monocytes is a crucial component of the generation of adipose tissue inflammation[27,35]. Circulating monocytes themselves are not a homogenous population and can be classified according to their expression of the cell surface markers CD14 and CD16. Classical monocytes (CD14++CD16−) are most prevalent (about 85 %), with the remainder composed of intermediate (CD14++CD16+; about 5 %) and non-classical monocytes (CD14+CD16++; about 10 %)[36]. The latter two subsets are considered to exhibit pronounced inflammatory properties, with gene expression profiling indicating greater pro-inflammatory cytokine production[37] and higher expression of the chemokine receptors C-X3-C-motif receptor 1 and C–C motif chemokine receptor type 5, the receptors for the chemokines fractalkine and regulated on activation, normal T cell expressed and secreted, respectively[36,38]. Accordingly, circulating numbers of CD16+ monocytes are elevated in several diseases including atherosclerosis[39–42]. With this in mind it is perhaps not surprising that obesity is also characterised by elevated numbers of circulating CD16+ monocytes compared with lean individuals[41,43] and marked reductions in circulating CD16+ monocyte populations are observed during weight loss, concomitant with reductions in intima-media thickness[43]. Additionally, waist circumference, a proxy of VAT, is also positively associated with circulating numbers of total monocytes and proportion of monocytes within the leucocyte fraction; similar relationships were found with the other leucocyte populations[43,44]. C–C motif chemokine receptor type 2 (the receptor for the chemokine monocyte chemotactic protein-1), C-X3-C-motif receptor 1 and C–C motif chemokine receptor type 5 expression on monocyte subsets are also reportedly higher in individuals with obesity compared with lean individuals[45,46].

As adipocytes undergo hypertrophic expansion, reduced tissue blood flow and impaired oxygen delivery creates areas of local tissue hypoxia[47,48]. Unlike other tissues, the hypoxic response in adipose tissue results in tissue fibrosis, rather than angiogenesis[24,49]. The associated metabolic overload and endoplasmic reticular stress within the tissue, in addition to instability of existing adipocytes and exhaustion of preadipocytes, results in activation of stress kinases including IκB kinase, c-jun N-terminal kinase and protein kinase R, which subsequently activate inflammatory signalling cascades[50]. The resulting upregulation of gene expression and secretion of pro-inflammatory cytokines and chemokines promotes significant monocyte recruitment and the subsequent accumulation of macrophages within adipose tissue to manage the remodelling of the extracellular matrix[4,50,51]. In support, in human subjects with overweight, incubation of adipose-tissue-derived endothelial cells with adipocyte-conditioned medium resulted in the upregulation of endothelial adhesion molecules and increased chemotaxis of isolated blood monocytes[52]. Furthermore, using a novel dynamic model of immune cell vascular adhesion and migration from the circulation that mimicked physiological blood flow, men with central obesity demonstrated greater *ex vivo* adhesion and migration of classical, intermediate and non-classical monocyte subsets, in addition to total monocytes expressing C–C motif chemokine receptor type 2 and C-X3-C-motif receptor 1, compared with men who were lean[53].

In obese human adipose tissue, over 90 % of the infiltrated macrophages are found surrounding dead and dying adipocytes in 'crown-like structures'[27,54]. Adipocyte death is positively correlated with BMI and adipocyte size in both SAT and VAT biopsies[54], with the density of crown-like structures greater in VAT[55], again supporting a greater contribution of VAT to a chronically inflamed state. Adipocyte death exhibits necrotic (rather than apoptotic) characteristics and appears to be regulated by the inflammatory signalling cascades activated by hypoxia, endoplasmic reticulum stress and exposure to TNF-α, reactive oxygen species and NEFA[25,54]. Activated macrophages fuse to form syncytia that scavenge cell debris and sequester exposed free adipocyte lipid droplets, ultimately forming multinucleate giant cells which can acutely produce IL-1 and TNF-α to further sustain to the inflammatory environment[54].

The health implications of obesity clearly do not simply stem from excess adipose tissue, but from the makeup and functioning of the adipose tissue and its constituent adipocytes and immune cells and their ability to respond to inflammatory cues in the local environment. As adipose tissue becomes more pro-inflammatory, it promotes a microenvironment that enhances local, systemic and cross-tissue inflammation, which fundamentally underpins disease risk. However, there is plasticity in this relationship and lifestyle modifications (e.g. physical activity and exercise) can mitigate obesity-associated inflammation.

Anti-inflammatory effects of physical activity in overweight and obesity

It is clear from the preceding section that excessive adiposity plays a fundamental role in the development of chronic inflammation. With this in mind, it would be intuitive that loss of adipose tissue would therefore

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reduce the capacity for adipocytes and tissue-resident immune cells to release inflammatory cytokines, thereby lowering the risk of developing cardiometabolic disease. This is certainly a valid rationale and given the role of physical inactivity in the development of obesity across the life course, interventions to increase activity levels and to help to reduce adipose tissue mass could be viewed as a relatively straightforward approach to help to reduce chronic inflammation. It is perhaps not surprising therefore that a recent systematic review of twenty-seven studies of exercise training interventions in people with overweight or obesity concluded that endurance training decreased circulating levels of IL-6, TNF-α levels and CRP levels, with TNF-α also reduced after resistance exercise[56]. Reductions in inflammatory biomarker levels often occurred concurrently with exercise training-induced weight-loss, yet reported decreases in IL-6 and TNF-α occurred independently of changes in body mass and/or fat mass in the majority of studies[56].

Physical activity and inflammation in obesity and overweight

There is a considerable body of evidence from the past 20 years from cross-sectional and longitudinal observational studies demonstrating that inflammatory biomarkers tend to be lower in people who are more physically active[57–61]. Changes in anthropometric measurements often follow a similar pattern to the changes in inflammatory biomarkers[60,61]. For example, a study of 1970 multi-ethnic men and women (50 % women) with mean BMI and waist circumference of 28·2 kg/m^2 and 98·4 cm, respectively, and who were free from clinically apparent CVD, used computed tomography to quantify abdominal VAT and SAT alongside inflammatory biomarkers and self-reported habitual physical activity[60]. After adjustment for age and sex, there was a dose–response relationship between quartiles for self-reported moderate-to-vigorous physical activity (MVPA) and inflammatory biomarkers, with IL-6 26 % lower and CRP 30 % lower for those in the highest quartile for MVPA (>6370 metabolic equivalents (MET) min/week) compared with those in the lowest quartile (<1830 MET min/week). Anthropometric measurements followed a similar trend, with those in the highest quartile for MVPA having a lower waist circumference, BMI, waist-to-hip ratio and SAT area and VAT area compared with those in the lowest quartile. This could be argued to indicate that inflammatory biomarkers were lower in the most active group simply because they had the least adipose tissue. However, after adjustment for SAT and VAT area, the two highest quartiles of MVPA were still associated with significantly lower levels of IL-6 compared with the lowest quartile[60].

While Vella *et al.*[60] examined self-reported MVPA and its relationship with inflammatory biomarkers in overweight and obesity, fewer studies have examined relationships between inflammatory biomarkers and objective markers of MVPA, light physical activity and time spent sedentary (time spent in a reclined, seated or lying position). This is despite time spent in light physical activity making up the greater proportion of time active for most adults[62]. Importantly, objective data using accelerometry and inclinometry suggest that both light physical activity and sedentary time also influence inflammatory biomarkers of cardiometabolic disease risk[61]. In a study of about 1600 middle-aged British men and women both MVPA (greater than three metabolic equivalent of tasks) *and* light physical activity (1·5–3 metabolic equivalent of tasks) were associated with lower circulating levels of IL-6 and CRP when adjusted for covariates including age, sex, socioeconomic status, smoking and long-term health issues including CVD[61]. Of note, the relationship persisted when further adjusted to take into account fat mass. Time spent sedentary (<1·5 metabolic equivalent of tasks) was also associated with higher circulating levels of IL-6 and CRP and again this was still apparent with adjustment for fat mass. The mediating role of adiposity in these relationships was also determined: fat mass contributed between 21 and 47 % of the total effects of each activity parameter on IL-6, with a greater contribution to the relationship in women than men, presumably owing to their higher fat mass for a given body index[63]. Similar findings were reported for CRP. This again supports the notion that while adiposity *per se* is undoubtedly a key mediator of the effect of physical activity and sedentary time on biomarkers of chronic inflammation, alterations in other factors within the adipose tissue itself, such as the ability of inflammatory immune cells to release pro-inflammatory cytokines, must also contribute.

Anti-inflammatory effects of physical activity on monocytes and ATM in overweight and obesity

There is a growing body of evidence supporting an 'anti-inflammatory effect' of physical activity and exercise that goes beyond loss of fat mass, with reductions in monocyte migration and macrophage accumulation in adipose tissue and a shift in circulating monocyte and tissue macrophage proportion and activation towards an anti-inflammatory phenotype suggested as contributing mechanisms and subsequent reductions in inflammatory cytokine production[64–66].

As detailed previously, obesity is associated with alterations in circulating monocyte subset distribution, with a significant monocytosis and shift in circulating populations towards a greater proportion of CD16+ monocytes[41,43]. Regular exercise is associated with lower total monocyte count[67], proportion of inflammatory (CD16+) monocytes and lipopolysaccharide (LPS)-stimulated monocyte TNF-α release[68]. In individuals with overweight and obesity 12 weeks of resistance exercise training reduced the proportion of CD16+ (intermediate and non-classical) monocytes by about one-third and was associated with reduced monocyte expression of Toll-like receptor-4, independent of weight-loss[69]. This is important as Toll-like receptor-4 activation results in downstream production of pro-inflammatory cytokines[70]. Regular exercise may also reduce obesity-induced monocyte activation; an 8-week high-intensity interval exercise programme reduced

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the activation of the intermediate monocyte subset, as assessed by human leukocyte antigen-DR (HLA-DR) expression, in individuals with insulin-resistance and obesity compared with lean individuals[71]. Again, this occurred in the absence of changes in weight and body composition. Further, in response to staphylococcal enterotoxin B stimulation *in vitro*, activation of both monocytes (CD86 and HLA-DR expression) and T-lymphocytes (CD-69 expression) was downregulated after a 6-month walking programme (30 min daily for five times weekly) in patients with non-dialysis chronic kidney disease (mean BMI 26·7 (SD 4·7) kg/m^2), compared with a usual care group of patients (mean BMI 29·0(SD 5·9) kg/m^2)[72]. This was accompanied by a concomitant reduction in the ratio of circulating IL-6 to IL-10 after 6 months while body weight and BMI remained stable. These studies emphasise once more that the mechanisms through which increases in physical activity positively impact chronic inflammation are not restricted to changes in adiposity.

While it is clear that increasing levels of activity can alter monocyte distribution and activation in individuals with overweight and obesity, the effect of activity levels on the migratory potential of peripheral monocytes into adipose tissue has received less attention, despite this process being a key contributor to the development of adipose tissue inflammation[27,35,41]. Physical activity may decrease the number and/or chemotactic efficiency of trafficking monocytes in obesity[73]; ten sessions of moderate-intensity exercise over a 2-week period (variety of walking, cycling and elliptical exercise increasing from 20 to 50 min over the programme) reduced expression of the chemokine receptors C–C motif chemokine receptor type 2 and C-X3-C-motif receptor 2 on CD16-expressing monocytes. This occurred in the absence of changes in circulating chemokine concentrations and body composition (including VAT mass). This may indicate that exercise reduces the potential for pro-inflammatory monocyte migration and therefore accumulation of pro-inflammatory monocytes into adipose tissue. In support, adjustment for MVPA and daily step count removed the difference in *ex vivo* monocyte tethering (modelling adherence to the endothelium) and migration in middle-aged males with central obesity compared with males who were lean[53]. This suggests that higher levels of physical activity can mitigate the negative effect of obesity on the movement of pro-inflammatory monocytes from the circulation to the tissues, providing support for a novel mechanism by which activity can lower chronic inflammation in obesity. A physical activity-mediated reduction in migratory potential of blood monocytes may account for the finding that macrophage infiltration into adipose tissue in mice fed with a high-fat diet for 16 weeks was lower in mice who were also exercised compared with those who were sedentary[33]. Macrophage infiltration expressed per g of adipose tissue was also significantly lower in the obese mice who exercised, compared with sedentary mice on the same diet, and similar to that of sedentary and exercised mice fed with a normal diet[33].

In summary, the importance of reducing adiposity to lower tissue and circulating markers of chronic inflammation and thus reduce cardiometabolic disease risk should not be overlooked. However, a growing body of evidence supports the concept that increasing levels of physical activity and lowering time spent sedentary reduces adipose tissue inflammation in obesity independently of changes in adiposity via direct effects on the inflammatory characteristics of monocytes and ATM. Therefore, increasing levels of physical activity can provide significant health benefits for those with overweight and obesity independent of weight loss.

How much physical activity is needed to lower chronic systemic inflammation?

The WHO guidance on the amount of physical activity needed for 'good health' in adults aged 18–65 years recommends at least 150 min of moderate-intensity aerobic physical activity or at least 75 min of vigorous-intensity aerobic physical activity (or an equivalent combination) throughout the week, in addition to muscle-strengthening activities on 2 or more days weekly[74]. While these evidence-based guidelines recommend the amount of physical activity required to offer significant health benefits and mitigate health risks, it is not an 'all or nothing' relationship, and for those beginning a journey to increase physical activity habits it is worth highlighting that any activity is better than no activity. This message may be more encouraging to those daunted or worried by the prospect of regular 'exercise' and disinclined to change behaviour. For example, using the UK Biobank database, participants with multimorbidity (≥2 chronic conditions) who engaged in higher volumes of physical activity (22 min of brisk walking daily) had a 71 % lower risk of mortality than those with multimorbidity who walked briskly for about 4 min daily[75]. However, brisk walking for just 10 min daily was associated with a 51 % lower risk of mortality for those with multimorbidity, and 60 % lower in those without multimorbidity[75]. The most prevalent conditions included hypertension and diabetes, in addition to cancer, depression and asthma and a greater proportion of multimorbid participants had overweight or obesity compared with participants without multimorbidity.

Specifically to biomarkers of inflammation, a 16-week intervention to reduce sedentary behaviour and improve walking time in individuals with increased cardiometabolic disease risk attenuated IL-1β and IL-6 release from LPS-stimulated circulating mononuclear cells and was associated with a trend for lower circulating IL-6 concentrations[76]. The strong inverse correlation between the change in walking time and attenuated cytokine production capacity followed a dose–response-like pattern, i.e. individuals who had the greatest increase in walking time demonstrated the strongest reduction in monocyte cytokine production, but decreases, albeit smaller, were still seen with increases in walking time of less than 30 min daily. Again, these responses occurred in the absence of changes in BMI[76]. In addition, as outlined earlier, both higher levels of light physical activity and lower sedentary time were associated with reduced circulating levels of IL-6 and CRP[61]. Importantly, these relationships

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were independent of an individuals' level of MVPA; in other words, the lower levels of biomarkers of inflammation in those engaged in more light physical activity or with less sedentary time was not because those individuals also engaged in more MVPA. This supports the notion that replacing sedentary time with any intensity of physical activity can reduce the development of chronic inflammation. This may be a more appealing message for individuals who are anxious or reluctant to become more active. It also emphasises that regardless of time spent in MVPA, sedentary behaviour is independently detrimental for the development of chronic inflammation; an important message for many of us who spend a significant proportion of the working week sat at a desk.

Conclusions

Chronic inflammation associated with obesity underlies the development of many long-term conditions, including cardiometabolic diseases such as CVD, stroke, non-alcoholic fatty liver disease, insulin resistance and type 2 diabetes. Hypertrophic adipose tissue creates local hypoxia and the resultant cellular stress, altered intracellular signalling and upregulation of pro-inflammatory cytokines promotes bone-marrow-derived blood monocyte recruitment into adipose tissue with the subsequent accumulation of pro-inflammatory macrophages. The continued disruption to adipose tissue immune and metabolic homoeostasis creates a cycle of inflammation and a persistent pro-inflammatory environment. Pro-inflammatory cytokines act both locally and 'spill-over' systemically leading to endothelial dysfunction and insulin resistance characteristic of many cardiometabolic diseases.

Increasing physical activity can dramatically lower levels of circulating inflammatory biomarkers. Exercise-induced loss of adipose tissue to reduce the major source of inflammatory cytokines and mediators undoubtedly contributes to this relationship. However, the mediating effect of higher levels of physical activity and lower sedentary time on the development of inflamed adipose tissue also occurs in the absence of changes in adiposity. This is important because current weight-loss interventions do not have a high success rate for sustained weight reduction, yet the message that weight loss is not necessary for the benefits of physical activity in lowering chronic inflammation and improving health should encourage those for whom losing weight is difficult. Furthermore, while greater benefits may be seen when achieving (or exceeding) the recommended physical activity guidelines for health, simply moving more appears to lower chronic inflammation. Reducing sitting time and increasing amounts of light physical activity may therefore provide a more approachable, practical and acceptable manner for some with overweight and obesity to become more active, reduce chronic inflammation and improve cardiometabolic health.

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Conflict of Interest

None.

Authorship

N. C. B. conceived the review article and content; N. C. B., M. J. R., A. J. W. and M. H. interpreted relevant literature, contributed to the writing of the article and reviewed drafts. All authors approved the final submission.

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