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How can physical activity facilitate a sustainable future? Reducing obesity and chronic disease

David J. Stensel[1,2,3,4]

[1]*School of Sport, Exercise and Health Sciences, National Centre for Sport and Exercise Medicine, Loughborough University, Loughborough, UK*

[2]*National Institute for Health and Care Research (NIHR), Leicester Biomedical Research Centre, University Hospitals of Leicester, National Health Service (NHS) Trust and the University of Leicester, Leicester, UK*

[3]*Faculty of Sport Sciences, Waseda University, Tokorozawa, Japan*

[4]*Department of Sports Science and Physical Education, The Chinese University of Hong Kong, Ma Liu Shui, Hong Kong*

This review examines the ways in which physical activity can contribute to a sustainable future by addressing significant public health issues. The review begins by identifying obesity and ageing as two major challenges facing societies around the world due to the association of both with the risk of chronic disease. Recent developments in the understanding and treatment of obesity are examined followed by an appraisal of the role of exercise alone and in combination with other therapies in preventing and managing obesity. The review then addresses the interaction between exercise and appetite due to the central role appetite plays in the development of overweight and obesity. The final section of the review examines the potential of physical activity to combat age-related chronic disease risk including CVD, cancer and dementia. It is concluded that while bariatric surgery and pharmacotherapy are the most effective treatments for severe obesity, physical activity has a role to play facilitating and enhancing weight loss in combination with other methods. Where weight/fat reduction via exercise is less than expected this is likely due to metabolic adaptation induced by physiological changes facilitating increased energy intake and decreased energy expenditure. Physical activity has many health benefits independent of weight control including reducing the risk of developing CVD, cancer and dementia and enhancing cognitive function in older adults. Physical activity may also provide resilience for future generations by protecting against the more severe effects of global pandemics and reducing greenhouse gas emissions via active commuting.

Ageing: Exercise: Energy balance: Sedentary behaviour

Two of the greatest challenges facing societies around the world in the 21st century are obesity and an ageing population. The prevalence of obesity has increased in children and adults over several decades in all regions of the world with no national success stories in countering this trend[1]. In the UK, 27 % of men and 29 % of

Abbreviations: GLP-1, glucagon-like peptide 1; PYY, peptide YY.

Corresponding author: David J. Stensel, email D.J.Stensel@lboro.ac.uk

women are currently living with obesity and a further 41 % of men and 31 % of women are classified as overweight[2]. In the United States it has been forecast that 48·9 % of adults (nearly one in two) will have obesity by 2030 with a prevalence above 50 % in twenty-nine states and not below 35 % in any state by 2030[3]. This is a concern due to the link between obesity and the risk of chronic disease notably type 2 diabetes the prevalence of which has increased in tandem with obesity rates[4,5]. The rising prevalence of type 2 diabetes has been exacerbated by the ageing of the population which may explain, at least in part, why over 25 % of adults in the United States have diabetes[4]. In 2009, Christensen and colleagues[6] estimated that '… most babies born since 2000 in … [developed countries] with long life expectancies will celebrate their 100th birthdays'. Although recent events (notably COVID-19) may have countered trends for increasing lifespan, the ageing of societies worldwide brings challenges for healthcare systems globally due to the close association between age and chronic diseases including heart disease, cancer, type 2 diabetes, chronic kidney disease and dementia. The prevalence of the latter of these, dementia, is forecast to increase in coming years mainly driven by increases in life expectancy[7]. Physical activity (and a subset of physical activity – planned, structured, 'exercise' for the development of physical fitness) has a key role to play in ameliorating these trends although the precise contribution of physical activity/exercise is a matter for debate and the subject of this review.

Obesity

Despite many decades of research and close to 100 000 journal papers with obesity in the title identified on PubMed (in January 2023), the precise causes of obesity and the best management/treatment strategies remain an area of controversy and vigorous debate. So much so that the Obesity Medicine Association recently published a Clinical Practice Statement 2022 addressing thirty obesity myths, misunderstandings and/or oversimplifications to assist clinicians in the care of people with obesity[8]. Gone are the days when obesity is simply attributed to an imbalance between energy intake and energy expenditure, notwithstanding views to the contrary[9]. Although, at the most basic level, the energy balance equation is still accepted by many (though not all) scientists working in obesity research, comprehensive reports[10] and excellent commentaries[11] detail how a wide variety of diverse but interrelated factors influence energy intake, energy expenditure and body composition. The Obesity Society[12] has identified sixty-six potential contributors to obesity which operate 'inside the person' or 'outside the person' to either increase energy intake, decrease energy expenditure or both. These contributors are broadly classified into seven categories: (1) environmental pressures on physical activity, (2) biological/medical, (3) maternal/developmental, (4) economic, (5) food and beverage behaviour/environment, (6) psychological and (7) social (Table 1).

Although some argue that we still do not have a clear explanation for the obesity epidemic[13] the prevailing view in the literature is that the primary driver of obesity is excess energy availability[14]. Some individuals are strongly genetically predisposed to obesity[15] while a small percentage are genetically resistant to it[16]. The genetic risk for obesity may be broadly classified into two categories: (1) monogenic obesity which is typically rare, early onset and involves single-gene defects, and (2) polygenic (common) obesity which involves hundreds of polymorphisms that each have a small effect. The central nervous system and neuronal pathways that control hedonic aspects of food intake (and hence body weight) are the main mechanisms underlying both monogenic and polygenic obesity[17].

The most effective treatment for obesity/severe obesity is bariatric surgery which can elicit 50–60 % excess weight loss for 10 years or more[18,19]. Pharmacotherapy for obesity is rapidly catching up due to the development of glucagon-like peptide 1 (GLP-1) receptor agonists[20–22] which effectively control food intake as demonstrated by recent trials with tirzepatide[23] and semaglutide[24–26]. The amylin analogue, cagrilintide, is also effective for weight loss[27] while antibody blockade of activin type II receptor signalling via bimagrumab promotes fat mass loss and simultaneously increases lean mass[28]. These developments herald a new era in pharmacotherapy for people with obesity[29].

After bariatric surgery and pharmacotherapy, diet has been shown to be effective for the prevention and management of obesity although long-term maintenance of weight loss with diet alone is a major issue. There is still disagreement on the most effective dietary strategy for weight control and recent debates about the carbohydrate insulin model[30–32] have the potential to confuse the public not to mention academics working in the field. Evidence to support the merits of any one dietary macronutrient for weight control is limited[33–35] while evidence to support another recent dietary trend, time-restricted eating, is mixed and inconclusive[36–38]. Physical activity/exercise has largely been relegated to the fourth line of 'defence' against overweight and obesity although some suggest that it has little value in this respect[39,40]. This will be examined in the next three sections the first of which addresses prevention.

Physical activity and prevention of obesity

Physical inactivity may be both a cause and a consequence of obesity. A large volume of observational evidence demonstrates that obesity prevalence/likelihood is associated with low levels of physical activity and/or high amounts of sedentary behaviour[41]. The cause-and-effect nature of this association is difficult to establish. Examples of such literature include studies examining energy expenditure in domestic tasks[42] and occupational activity[43] as well as studies of time spent in sedentary pursuits[44]. Archer and colleagues[42] examined time-use diary data to quantify household management energy expenditure from 1965 to 2010 in adult women (aged

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Table 1. Potential* contributors to obesity

Potential contributor	Potential mechanism	↑ EI	↓ EE	Both?
Environmental pressures on physical activity	Living in crime-prone areas (O)			✓
	Consistent temperature (i.e. air conditioning/heating, thermoregulation) (O)		✓	
	Increased sedentary time (i.e. inactive leisure 'screen' time, inactive job requirements) (O)		✓	
	Built environment (i.e. stairwell design/access, building design, absence of or poor sidewalks) (O)		✓	
	Decreased opportunity for non-exercise based physical activity (i.e. driving *v.* walking to work and school, sedentary jobs) (O)		✓	
	Labour saving devices (O)		✓	
Biological/medical	Hyper-reactivity to environmental food cues (I)	✓		
	Heightened hunger response (I)	✓		
	Delayed satiety (I)	✓		
	Environmental/chemical toxins (O)	✓		
	Age-related changes (i.e. menopause, mobility decline, hormones) (I)			✓
	Chronic inflammation (i.e. altered insulin signalling and glucose homoeostasis) (I)			✓
	Pathological sources of endocrine dysregulation (i.e. thyroid dysfunction, polycystic ovary syndrome, Cushing's syndrome) (I)			✓
	Genetic and epigenetic factors (I)			✓
	Central and peripheral regulators of appetite and adipose tissue (I)			✓
	Infection (i.e. human adenovirus 36) (O)			✓
	Weight gain inducing drugs (O)			✓
	Smoking cessation (O)			✓
	Sleep deficits (O)			✓
	Thermogenesis (I)		✓	
	Gut microbiota (I)		✓	
	Pain sensitivity (I)		✓	
	Physical disabilities (I)		✓	
Maternal/developmental	Gestational diabetes (I)			✓
	Maternal employment (O)			✓
	Breast-feeding and/or related factors (O)			✓
	Maternal stress (O)			✓
	Maternal smoking (O)			✓
	Maternal obesity (O)			✓
	Delayed prenatal care (O)			✓
	Birth order (first-born in family) (O)			✓
	Having children (in women) (O)			✓
	Non-parental childcare (O)			✓
	Maternal over-nutrition during pregnancy (O)			✓
	Birth by C-section (O)			✓
	Pre-natal air pollution (O)		✓	
Economic	Market economy (O)	✓		
	Food surplus (O)	✓		
	Pervasive food advertising (O)	✓		
	Westernisation and economic development (O)			✓
	Low socioeconomic status and nutrition support (O)			✓
Food and beverage behaviour/ environment	Increased availability of energy dense, nutrient poor foods and beverages (O)	✓		
	Lack of nutritional education (O)	✓		
	Diet patterns (O)	✓		
	Eating away from home (O)	✓		
	Larger portion sizes (O)	✓		
	Skipping meals (O)	✓		
	Lack of family meals (O)	✓		
	Eating as recreation, snacking, special occasions (O)	✓		
	Food insecurity (O)	✓		
Psychological	Disordered eating (night eating syndrome, binge eating, 'food addiction') (I)	✓		
	Emotional coping (I)	✓		
	Self-regulatory and coping deficits (I)			✓
	Mood disturbance (i.e. depression, anxiety, bipolar, etc.) (I)			✓
	Trauma history (I)			✓
	Mental disabilities (I)			✓
	Stress (O)			✓
	Child maltreatment (O)			✓

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	Weight cycling (yo-yo dieting) (O)		✓
	Social anxiety (i.e. exercise avoidance) (I)	✓	
Social	Family conflict (O)		✓
	Social networks (O)		✓
	Weight bias and stigma (i.e. avoidance of medical care, self-esteem, teasing history) (O)		✓
	Entering a romantic relationship (O)		✓
	Lack of employer preparedness to assist with obesity (O)		✓
	Lack of health care provider support/knowledge and inadequate access to care (O)		✓

EI, energy intake; EE, energy expenditure.
*Potential contributors indicate anything that has been put forth in the research literature as a question of investigation and is not intended to be a verification of whether; or the extent to which, each may or may not contribute.
The column headed 'Both?' indicates factors that may increase energy intake and decrease energy expenditure, or the effect is unknown.
(I) Indicates that the factor operates inside (within) the person.
(O) Indicates that the factor operates outside of the person.
Adapted from The Obesity Society (2015).

19–64 years) living in the United States. They estimated that household management energy expenditure decreased by 42 % in non-employed women and 30 % in employed women across this time – equivalent to a decrement of 10·5 MJ/week (2518 kcal/week) or 1·5 MJ/d (360 kcal/d) in non-employed women and 3·9 MJ/week (923 kcal/week) or 0·55 MJ/d (132 kcal/d) in employed women. They observed that much of this reduction in 'active pursuits' (i.e. housework) was reallocated to sedentary pastimes (e.g. watching TV) and concluded that this could have contributed to the increase in obesity prevalence in women in the United States between 1965 and 2010. Similarly, Church and colleagues[43] examined occupation-related physical activity over nearly five decades (1960–2006) in United States adults (aged 40–50 years) using data from the National Health and Nutrition Examination Surveys. They estimated that occupation-related energy expenditure decreased by 594 kJ/d in men during this time and this was sufficient to explain an increase in body mass from 77 kg at baseline to 90 kg at follow-up which closely matched the actual increase in body mass (77–92 kg) during this period. Similar trends were observed in women in this study. Another study employing National Health and Nutrition Examination Survey data[44] has demonstrated a positive association between prolonged sedentary time and waist circumference (a marker for central adiposity) in adults, while a recent review of twenty-one observational studies examining physical activity levels among pregnant women concluded that active pregnant women gain less weight during pregnancy than inactive pregnant women[45].

A rather novel study design employed to examine the influence physical activity on body composition is the study of monozygotic (identical) twins discordant for physical activity[46]. This 'natural experiment' involved comparisons of seventeen Finnish twin pairs found to be discordant for physical activity over a prolonged period. The twins with higher physical activity were shown to have lower body fat, visceral fat and liver fat than their less active counterparts. Another interesting and thought-provoking study conducted by Levine and colleagues[47] examined non-exercise activity thermogenesis, i.e. the energy expended in posture and movement associated with the routines of daily life (excluding energy expended through purposeful exercise). Inclinometers and triaxial accelerometers were used to assess time spent lying, siting, standing and ambulating in ten lean individuals and ten individuals with obesity over a 10-d period resulting in about 25 million data points on posture and movement for each person. Doubly labelled water was used to quantify energy expenditure. The group classified with obesity was found to sit for 2 h longer each day than the group classified as lean. It was estimated that the difference in non-exercise activity thermogenesis between groups equated to 1464 kJ/d. Interestingly all individuals participating in this study (from both groups) were self-proclaimed 'couch potatoes'. Posture allocation did not change after an 8-week intervention during which the lean group gained weight by overfeeding and the group with obesity lost weight by energy restriction. This raises the intriguing possibility that non-exercise activity thermogenesis is 'biologically determined'[47] and resistant to change although this research is limited by a small sample size and a relatively short follow-up period.

The finding that people with obesity are generally less active than people who are lean leads to the assertion that increases in physical activity can be helpful for preventing and managing obesity, but Pontzer and colleagues have conducted a series of studies over the past decade countering this proposition[48–54]. These studies have employed the doubly labelled water technique to assess energy expenditure in various human and primate groups. One such study[48] demonstrated that although the physical activity level of Hadza hunter–gatherers was higher than that of Westerners, total daily energy expenditure did not differ between groups after accounting for differences in body size. Pontzer and colleagues concluded that 'the similarity in metabolic rates across a broad range of cultures challenges current models of obesity suggesting that Western lifestyles lead to

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decreased energy expenditure'[48]. Another study by Pontzer's group observed similar levels of energy expenditure in wild and captive primate populations in contrast to the expectation that wild primates would be more active[49]. In view of such findings Pontzer proposed a Constrained Total Energy Expenditure hypothesis stating 'rather than increasing with physical activity in a dose-dependent manner, experimental and ecological evidence suggests … total energy expenditure is a relatively constrained product of our evolved physiology'[50]. This hypothesis was supported by a study of 322 adult human subjects living in five populations which found that although physical activity was positively correlated with total energy expenditure this relationship was much stronger at low levels of energy expenditure and plateaued in the upper range of physical activity[51]. Pontzer hypothesised that in contrast to primate groups human subjects utilise a greater portion of their energy expenditure to fuel their larger brains and that human subjects have a greater predisposition to accumulate adipose tissue which is an advantage for their evolution[52].

More recently, Pontzer's group has used longitudinal data from The International Atomic Energy Agency doubly labelled water database to demonstrate that 'energy compensation' occurs when physical activity levels are elevated, i.e. basal energy expenditure is reciprocally reduced[53]; and that low adjusted total energy expenditure does not predict gains in body fat over time, and higher adjusted total energy expenditure does not protect against weight gain[54]. Collectively, the work of Pontzer and colleagues is provocative and may suggest that physical activity/exercise will be ineffective for the prevention/management of obesity. In contrast, exercise has been shown to be effective for weight loss in laboratory-based studies of people with obesity, and physical activity may have a role to play in weight loss maintenance as will be explored in the next section.

Physical activity and management of obesity

There is good evidence from randomised controlled trials that exercise is effective for reducing body mass and body fat in people with overweight/obesity. A notable example is a 12-week randomised controlled trial study conducted by Ross and colleagues[55] comprising four study groups: (1) control, (2) diet-induced weight loss, (3) exercise-induced weight loss and (4) exercise without weight loss. Participants in the diet-induced weight loss group reduced their energy intake by 2929 kJ/d while those in the exercise-induced weight loss group maintained their usual energy intake and expended 2929 kJ/d in exercise (brisk walking or light jogging). Body mass decreased by 7·5 kg (8 %) in both weight loss groups with a greater reduction in body fat in the exercise-induced weight loss group. There were similar reductions in visceral adipose tissue in both weight loss groups and some reduction in visceral adipose tissue also in the exercise without weight loss group. The authors concluded that physical activity without energy restriction substantially reduces obesity – particularly abdominal obesity[55]. Ross and colleagues subsequently published a review of eight studies which directly compared diet and exercise interventions for weight loss concluding that 'exercise without diet restriction is an effective strategy for reducing obesity and related co-morbidities' and recommending 45–60 min of moderate intensity exercise each day[56]. This is broadly consistent with the recommendations of the American College of Sports Medicine Position Stand on Appropriate Physical Activity Intervention Strategies for Weight Loss and Prevention of Weight Regain in Adults, i.e. 150–250 min/week of moderate intensity exercise to prevent weight gain/provide modest weight loss and >250 min/week of moderate intensity exercise to elicit clinically significant weight loss[57].

Although physical activity alone can produce substantial and clinically significant weight loss it is important to note that this is not the norm. Indeed, a recent review of twelve systematic reviews involving 149 studies concluded that exercise training interventions typically induce weight loss of 1·5–3·5 kg[58]. Various factors may explain this modest weight loss including metabolic and behavioural compensation. Metabolic compensation occurs via physiological changes in metabolism while behavioural compensation relates to changes in dietary and exercise behaviours to 'compensate' for the perturbation in energy balance caused by the intervention. (The term 'behavioural compensation' is controversial because changes in 'behaviour' may be determined by physiological/metabolic factors.) Dhurandhar and colleagues estimate that exercise studies typically result in 55–64 % less weight loss than expected due to compensation[59]. Consistent with this prediction are the findings of a recent study showing that treadmill/cycling exercise over a 24-week period induced only half the expected weight loss in adult men and women with obesity due to reductions in 24-h energy expenditure, i.e. RMR and/or non-exercise activity thermogenesis[60].

Aside from metabolic compensation another, under-researched, factor which is rarely assessed in energy balance studies is energy excretion, i.e. consumed food which is excreted in faeces or filtered through the kidneys. The routinely used kilocalorie equivalents per g of carbohydrate, fat and protein are 4, 9 and 4, respectively. These represent the 'metabolisable energy' per unit of mass for a given macronutrient but there is variability between individuals in the extent to which full oxidation of metabolisable energy occurs and this variation is due (at least in part) to differences in fat faecal excretion. This can average between 0·5 and 5 % of energy intake with an interindividual variation of 2–9 %[61]. Whether energy excretion changes during exercise interventions is unknown but it is feasible that it could, and this would be another source of compensation reducing the effectiveness of the intervention. Nearly 30 years ago, Bouchard and colleagues[62] demonstrated that some people lose more weight, body fat and visceral fat than others in response to exercise. In their study average exercise-induced weight loss among seven pairs of identical twins after a 93-d exercise intervention (2 h each day, 9 out of every 10 d) was 5 kg, but weight loss ranged from

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<2 kg to about 8 kg. There was less variation in response within twin pairs than there was between twin pairs suggesting that responses to exercise are determined, at least in part, by genetic factors. More recent studies have confirmed that there is interindividual variability in body composition changes in response to exercise[63,64] although the precise contribution of genetic and environmental factors to this variability remains to be identified.

Although exercise alone can induce weight loss in people with obesity it should ideally be used in combination with other therapies. It has been shown that the combination of high-intensity interval training and time-restricted eating induce superior reductions in total and visceral fat than either intervention alone[65]. Similarly, the combination of exercise and liraglutide therapy improved healthy weight/fat loss (achieved via energy restriction) more than either therapy alone[66]. This latter study highlights that exercise has an important role to play in the maintenance of long-term weight loss as an adjunct to other therapies including bariatric surgery and pharmacotherapy[19]. The challenge of maintaining long-term weight loss is made particularly difficult due to metabolic adaptation induced by changes in hormones that influence appetite[67] and there is evidence that exercise may assist with long-term weight loss by improving appetite regulation[68], an issue examined in the next section.

Exercise and appetite

There has been a proliferation of interest in the relationship between physical activity/exercise and appetite in recent decades. Research examining this relationship has been facilitated by an expansion of research and understanding of the factors influencing food preferences[69], the physiological mechanisms controlling eating and different types of eating, i.e. deficit-induced eating, habitual eating and opportunistic eating[70], and the factors contributing to satiation and meal termination[71]. For centuries the hypothalamus has been the centre of attention as a key regulator of appetite[72] and within the arcuate nucleus of the hypothalamus, agouti-related peptide neurones are thought to govern the drive to eat[73]. A key hormone influencing agouti-related peptide neuronal activity is ghrelin which has attracted widespread attention due to its unique role in stimulating hunger and food intake[74]. Aside from ghrelin many other hormones influence appetite mostly with appetite suppressing effects; these include leptin, peptide YY (PYY), insulin, pancreatic polypeptide, amylin, oxyntomodulin, cholecystokinin, GLP-1 and adiponectin[74]. The most widely studied of these in relation to exercise are ghrelin, PYY and GLP-1 due to the potency with which these hormones act on appetite and their relative ease of measurement. Due to the crucial role appetite plays in the development of overweight and obesity it is essential to understand how exercise affects appetite and hence the most effective way to implement exercise as a therapy for obesity.

The effects of physical activity on the regulation of appetite and food intake have been extensively reviewed[75–77] and may be broadly categorised as acute (responses to a single bout of exercise) and chronic (responses to exercise training) effects. Most research in human subjects has focused on the peripheral (hormonal) influences of exercise rather than central (brain) responses although some evidence is available in relation to the latter[77]. Single bouts of exercise induce a short-term energy deficit without stimulating compensatory increases in appetite or food intake. Many studies have shown that vigorous-intensity acute exercise suppresses ghrelin, notably the active form of the hormone – acylated ghrelin – while simultaneously increasing concentrations of GLP-1 and PYY[75]. Responses are generally consistent in groups who are lean and those with obesity. For example, Douglas and colleagues[78] demonstrated that total GLP-1 and total PYY were increased in both groups during the hours after treadmill exercise and these elevations coincided with suppressed appetite perceptions. Simply interrupting sitting with short breaks of brisk walking elevates total GLP-1 and total PYY as demonstrated by a recent acute study involving men and women with central overweight/obesity[79]. Exercising in a fasted, rather than fed, state is more effective for eliciting a short-term decrease in energy intake but may lead to increased hunger subsequently[80]. Individual variability in appetite perceptions and appetite-related hormone (acylated ghrelin, total PYY) responses to exercise has been demonstrated using a robust replicated crossover design suggesting some individuals will experience greater appetite suppressing effects from acute exercise than others[81].

The significance of acute changes in appetite and appetite-related hormones for long-term weight management is uncertain. In theory, if the acute appetite suppressing responses to exercise were repeated regularly this would lead to long-term reductions in appetite and food intake but evidence to support this hypothesis is limited due to the difficulty of performing well-controlled intervention studies with accurate measures of free-living food intake. Indeed, with repeated energy deficits created through exercise some form of compensation is likely to occur and there is evidence that attentional bias towards food cues is increased in response to acute exercise[82]. At least one chronic exercise study conducted by a prolific group of appetite researchers at the University of Leeds has suggested a 'dual-process action' of exercise on appetite control[83]. This study involved a 12-week, laboratory based, supervised exercise intervention (energy expenditure = 10 460 kJ/week) in fifty-eight men and women with overweight/obesity. The intervention resulted in an average weight loss, fat mass loss and waist circumference reduction of 3·2 kg, 3·2 kg and 5 cm, respectively[83]. There was an increase in fasting hunger but an increase also in the satiety quotient of a breakfast meal (calculated by the change in appetite scores relative to meal content). The authors concluded that while exercise-induced weight loss increased the drive to eat it also enhanced the satiating effect of a fixed meal[83].

The Leeds group has also conducted two innovative studies examining energy balance with differing levels of energy expenditure in men and women[84,85]. The

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first of these used a within-subject, repeated measures design to compare energy intake and balance over 7 d in six lean women across three interventions: control (0 MJ/d), medium exercise level (1·9 MJ/d) and high exercise level (3·4 MJ/d). Participants self-weighed their *ad libitum* food intake while energy expenditure was estimated using continuous heart rate monitoring. Daily energy expenditure increased across conditions: 9·2, 11·0 and 12·1 MJ/d for control, medium exercise level and high exercise level, respectively. The corresponding values for energy intake were 8·9, 9·2 and 10·0 MJ/d. It was concluded that increasing energy expenditure through exercise led to significant but partial compensations in energy intake (about 33 % of the energy expenditure due to exercise) and that accurate adjustments in energy intake to acute increases in energy expenditure would take weeks rather than days[84]. A second 7-d study by the Leeds group employed a whole-body indirect calorimeter to examine energy expenditure responses to sedentary (1·4 × RMR) and moderately active (1·8 × RMR) conditions in men while energy intake was continuously monitored. Energy expenditure was 9·7 MJ/d in the sedentary trial and 12·8 MJ/d in the moderately active trial. Corresponding values for energy intake were 13·5 and 14·4 MJ/d, respectively. Thus, energy intake was higher than energy expenditure in both trials, but cumulative energy balance was 2·4 times higher in the sedentary trial (26·3 MJ) than the moderately active trial (11·1 MJ) causing the authors to conclude that a sedentary routine does not induce compensatory reductions in energy intake, leading to a positive energy balance, most of which is stored as fat[85].

The studies outlined earlier conducted by the Leeds group provide valuable information on the effects of exercise on energy balance but their application to the field of obesity is limited because participants in these studies were lean. More recently, members of the Leeds research group in collaboration with other researchers have conducted a systematic review and meta-analysis examining the effects of exercise training interventions on energy intake and appetite control in adults with overweight and obesity[86]. Forty-eight relevant articles were identified, and it was concluded that exercise training in people with overweight or obesity does not induce a substantial change in food intake or appetite during the period of training although it was acknowledged that the self-report nature of the food intake data and the small number of studies rated as fair or good quality were limitations.

Recent decades have seen a proliferation of research and understanding about the effects of exercise on appetite. Much of this has focused on hormonal control of appetite which clearly provides only partial understanding. Methods to quantify energy intake under free-living conditions remain woefully inadequate and technological developments for non-intrusive assessment of energy intake are essential to address this. It is also clear that a variety of endocrinology factors beyond the most frequently studied appetite-related gut hormones (i.e. ghrelin, GLP-1, PYY) play a role in the interaction between exercise and appetite. These include the recently discovered blood-borne signalling metabolite *N*-lactoyl-phenylalanine which is associated with reduced food intake[87], various myokines[88], growth differentiation factor 15[89], lactate[90], orexin and serotonin[91] and a newly proposed 'gravitostat' operating via a sensor released from osteocytes[92]. We are also learning more about how genetic factors, exercise and appetite interact. For example, there is a potentially greater benefit of exercise in those with obesity risk variants of the fat mass and obesity associated (FTO) gene[93–95]. Further study of these issues is crucial to provide a more complete understanding of how exercise and appetite interact. At the beginning of this section, it was noted that the hypothalamus is central to appetite control and more research in this area is vital. Recent evidence from animal studies suggests that exercise may beneficially modify anorexigenic signals and food intake via mechanisms involving myokines released during muscle contraction and a reduced central anti-inflammatory response[77] but there is a need for longitudinal studies in human subjects to better understand how exercise affects hypothalamic regulation of appetite.

Physical activity, ageing and chronic disease

So far, this review has focused on the therapeutic potential of physical activity in relation to obesity due to the prolonged upward trend in the prevalence of this condition globally and the ensuing public health burden. Aside from obesity there is a wealth of evidence to support the benefits of physical activity for the prevention and management of chronic diseases associated with ageing, most notably CVD, cancer, and type 2 diabetes among others[96,97]. Knowledge and understanding about the mechanisms by which physical activity interacts with chronic disease risk is accumulating at pace. Many 'exerkines' (signalling moieties released in response to acute/chronic exercise) have been identified. These exert their effects through endocrine, paracrine and autocrine pathways involving multiple organs, cells and tissues including skeletal muscle (myokines), the heart (cardiokines), liver (hepatokines), white adipose tissue (adipokines), brown adipose tissue (baptokines) and neurones (neurokines) and have the potential to assist in the prevention and management of chronic disease[98]. Future decades are likely to see profound increases in our mechanistic understanding in relation to physical activity and chronic disease.

The field of accelerometer-based wearable devices has facilitated important advances in the quality of research linking physical activity/inactivity with all-cause mortality and chronic disease risk. Recent examples include: (1) a report from the UK Biobank (78 500 participants followed for a median of 7 years) demonstrating an association between higher daily step count and a lower risk of all-cause mortality, CVD mortality and cancer mortality as well as a lower incidence of CVD and cancer up to a threshold of approximately 10 000 steps daily[99], (2) a report from the coronary artery risk development in young adults study showing that those who took 7000

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or more steps/d experienced a lower mortality rate than those taking <7000 steps/d – an association which held in Black and White men and women[100], (3) an estimation using accelerometer data from the National Health and Nutrition Examination Survey that 110 000 deaths per year could be avoided if United States adults aged 40–85 years or older increased their moderate-to-vigorous intensity physical activity by 10 min/d, a finding which applied in all groups studied, i.e. Mexican American, non-Hispanic Black and non-Hispanic White adults[101] and (4) a report from the *All of Us* Research Program in the United States that higher daily step counts are associated with a lower risk of various conditions including obesity, sleep apnoea, gastroesophageal reflux disease, diabetes and hypertension[102].

The past decade has seen increased focus on the adverse health effects of sedentary behaviour specifically and independently of overall physical activity levels. A recent publication, for example, involving over 105 000 men and women followed for a median of 11·1 years, observed that sitting for ≥8 h/d compared with sitting for <4 h/d was associated with an increased risk of all-cause mortality and CVD events and this association was stronger in low-income and lower-middle-income countries than in high-income and upper-middle income countries[103]. Such findings confirm earlier reports from the community based Kungsholmen Project in Stockholm, Sweden, that physical activity is an essential healthy lifestyle component associated with extended mortality where benefits are maintained even in those in their 70s and 80s[104]. These and other studies demonstrate the potential for lowering chronic disease burden through increased physical activity and reduced sedentary behaviour. An analysis by Lee and colleagues[105] incorporating population attributable fractions associated with physical inactivity estimates that worldwide physical inactivity causes 6 % of heart disease, 7 % of diabetes, 10 % of breast cancer, 10 % of colon cancer and 9 % of premature mortality. According to the calculations of Lee and colleagues, decreasing global physical inactivity by 25 % could avert 103 million deaths/year worldwide[105].

Perhaps the disease most closely linked to ageing is dementia. Here again, evidence is accumulating to support the therapeutic potential of physical activity. A notable study is the 1-year randomised controlled trial conducted by Erickson and colleagues[106] which investigated hippocampus shrinkage in late adulthood due to its association with impaired memory and dementia risk. In this trial 120 women and men (mean age 67 years) were randomly allocated to either a walking intervention group or a stretching control group. Walking increased left and right hippocampus volume (assessed by MRI) by 2 % while volumes declined in the control group. It was estimated that walking reversed age-related hippocampus volume loss by 1–2 years. Increases in hippocampus volume were correlated with increases in fitness (maximum oxygen uptake), increases in serum concentrations of brain-derived neurotrophic factor, a mediator of neurogenesis, and increases in memory performance. It was concluded that aerobic exercise training is effective for reducing hippocampal volume loss and improving memory function in late adulthood.

The implication of the study by Erickson and colleagues[106] is that exercise may reduce the risk of developing dementia, or at least delaying the onset of dementia. Many studies support this contention. Recent examples include a report from the Chicago Health and Ageing Project[107] which developed a healthy lifestyle score based on five modifiable lifestyle factors: healthy diet, regular physical activity, participation in late life cognitive activities, non-smoking and light-to-moderate alcohol consumption. Participants with four or five healthy factors lived longer and lived a larger proportion of their remaining years without Alzheimer's dementia than those with zero or one healthy lifestyle factor. This is one of many studies suggesting that physical activity, as part of a 'package' of healthy lifestyle factors, has potential for reducing dementia risk. The extent to which physical activity alone (independent of other healthy lifestyle factors) can reduce the risk of dementia is debatable but data from the UK Biobank[108] (78 430 adults aged 40–79 years followed for 6·9 years) reveal that higher accelerometer-derived step count is associated with a lower risk of all-cause dementia. The optimal dose in this report is just under 10 000 steps/d and stronger associations were noted when steps were performed at a higher intensity.

The associations between physical activity, sedentary behaviour and chronic disease risk described earlier suggest there may be great benefit in encouraging middle-aged and older adults to maintain/increase their physical activity levels and reduce the amount of time spent sedentary. This may be particularly important in those aged 60 years and above. A recent analysis of daily energy expenditure through the life course employing doubly labelled water assessments in over 6400 males and females (aged between 8 d and 95 years) from twenty-nine countries found energy expenditure was stable between 20 and 60 years of age but a gradual decline occurs after age 60[109]. As has been noted 'it cannot be coincidence that the increase in incidence of non-communicable diseases and disorders begins in this same time frame'[110]. More research is required to understand the extent to which the decline in physical activity/energy expenditure beyond age 60 is biologically determined and immutable and the extent to which it is amenable to change by conscious effort.

Conclusions

Evidence presented in this review shows that promotion of physical activity is a vital component of a wider strategy to secure a sustainable future. Although the precise contribution of physical activity to preventing overweight and obesity remains a topic of debate there is a wealth of evidence suggesting it is an important factor. Physical activity has a key role to play in the management of obesity either by assisting with initial weight loss (in combination with dietary restriction) or by helping to maintain weight loss induced by bariatric surgery and/or pharmacotherapy. Recent evidence demonstrates

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that behavioural weight management programmes, which include physical activity as a component, can have long-lasting effects[111,112]. Notwithstanding such evidence, some have proposed a 'weight-neutral' strategy for obesity treatment where physical activity is promoted due to a multitude of other benefits aside from effects on weight[113]. These include reducing the risk of CVD and cancer incidence and mortality, and important roles in the prevention and management of other conditions including hyperglycaemia[114] and depression[115].

Much has been learned about the relationship between exercise and appetite in recent years. Contrary to the view sometimes promoted that exercise enhances appetite causing overeating, there is limited scientific evidence to support this. Not examined in this review is the interaction between exercise, sleep and appetite. This is certainly an area for future research due to exciting findings showing that sleep extension in short sleepers may be effective for reducing energy intake and weight[116].

The recent COVID-19 global pandemic is another factor to consider when planning for a sustainable future. Obesity emerged as a major risk factor for hospitalisation and death due to COVID-19[117] while physical activity was identified as a factor protecting against severe COVID-19[118]. Promotion of physical activity across all sections of the population would seem sensible for protection from future pandemics. Finally, physical activity as a means of active transport has a role to play in combating climate change, possibly the greatest threat to humanity at present, by reducing greenhouse gas emissions[119].

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Conflict of Interest

None.

Authorship

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References

1. Ng M, Fleming T, Robinson M *et al.* (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis of the global burden of disease study 2013. *Lancet* **384**, 766–781.
2. Baker C (2022) Obesity Statistics. Commons Library Research Briefing, 16 March 2022. https://commonslibrary.parliament.uk/research-briefings/sn03336/.
3. Ward ZJ, Bleich SN, Cradock AL *et al.* (2019) Projected U.S. state-level prevalence of adult obesity and severe obesity. *N Engl J Med* **381**, 2440–2450.
4. Polonsky KS (2012) The past 200 years in diabetes. *N Engl J Med* **367**, 1332–1340.
5. Wang L, Li X, Wang Z *et al.* (2021) Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999–2018. *JAMA* **326**, 704–716.
6. Christensen K, Doblhammer G, Rau R *et al.* (2009) Ageing populations: the challenges ahead. *Lancet* **374**, 1196–1208.
7. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P *et al.* (2017) Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. *Br Med J* **358**, 1–15, doi.org/10.1136/bmj.j2856.
8. Bays HE, Golden AE & Tondt J (2022) Thirty obesity myths, misunderstandings, and/or oversimplifications: an Obesity Medicine Association (OMA) clinical practice statement (CPS) 2022. *Obes Pillars* **3**, 100034, doi.org/10.1016/j.obpill.2022.100034.
9. Doroghazi RM (2015) A candid discussion of obesity. *Am J Med* **128**, 213–214.
10. Foresight (2007) Tackling obesities: future choices – obesity report. The Stationery Office, London. http://www.foresight.gov.uk/Obesity/obesity_final/Index.html (assessed 21 October 2022).
11. Dhurandhar NV, Petersen KS & Webster C (2021) Key causes and contributors of obesity: a perspective. *Nurs Clin N Am* **56**, 449–464.
12. The Obesity Society. Potential Contributors to Obesity Infographic. https://www.obesity.org/wp-content/uploads/2020/05/TOS-Reasons-for-obesity-infographic-2015.pdf (assessed 21 October 2022).
13. Mozaffarian D (2022) Perspective: obesity – an unexplained epidemic. *Am J Clin Nutr* **115**, 1445–1450.
14. Barrera EL & Shively G (2022) Excess calorie availability and adult BMI: a cohort analysis of patterns and trends for 156 countries from 1890 to 2015. *Food Policy* **109**, 102271, doi.org/10.1016/j.foodpol.2022.102271.
15. Bouchard C (2021) Genetics of obesity: what we have learned over decades of research. *Obesity* **29**, 802–820.
16. Riveros-McKay F, Mistry V, Bounds R *et al.* (2019) Genetic architecture of human thinness compared to severe obesity. *PLoS Genet* **15**, e1007603, doi.org/10.1371/journal.pgen.1007603.
17. Loos RJF & Yeo GSH (2021) The genetics of obesity: from discovery to biology. *Nat Rev Genet* **23**, 120–133.
18. Eisenberg D, Shikora SA, Aarts E *et al.* (2022) 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and metabolic disorders (IFSO): indicators for metabolic and bariatric surgery. *Surg Obes Relat Dis* **18**, 1–12. https://asmbs.org/app/uploads/2022/10/ASMBS-IFSO-Guidelines-2022-PIIS1550728922006414.pdf.
19. Kheniser K, Saxon DR & Kashyap SR (2021) Long-term weight loss strategies for obesity. *J Clin Endocrinol Metab* **106**, 1854–1866.
20. Brown E, Heerspink HJL, Cuthbertson DJ *et al.* (2021) SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indicators. *Lancet* **398**, 262–276.

https://doi.org/10.1017/S0029665123002203 Published online by Cambridge University Press

21. Drucker DJ (2022) GLP-1 physiology informs the pharmacotherapy of obesity. *Mol Metab* **57**, 101351, doi.org/10.1016/j.molmet.2021.101351.
22. Kumar N & D'Alessio DA (2022) Slow and steady wins the race: 25 years developing the GLP-1 receptor as an effective target for weight loss. *J Clin Endocrinol Metab* **107**, 2148–2153.
23. Jastreboff AM, Aronne LJ, Ahmad NN *et al.* (2022) Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* **387**, 205–216.
24. Wadden TA, Bailey TS, Billings LK *et al.* (2021) Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioural therapy on body weight in adults with overweight or obesity. The STEP 3 randomised clinical trial. *JAMA* **325**, 1403–1413.
25. Wilding JPH, Batterham RL, Calanna S *et al.* (2021) Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* **384**, 989–1002.
26. Weghuber D, Barrett T, Marrientos-Perez M *et al.* (2022) Once-weekly semaglutide in adolescents with obesity. *N Engl J Med* **387**, 2245–2257.
27. Lau DCW, Erichsen L, Francisco AM *et al.* (2021) Once-weekly cagrilintide for weight management in people with overweight and obesity: a multi-centre, randomised, double-blind, placebo-controlled and active-controlled, dose-finding phase 2 trial. *Lancet* **398**, 2160–2172.
28. Heymsfield SB, Coleman LA, Miller R *et al.* (2021) Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity. A phase 2 randomised controlled trial. *JAMA Netw Open* **4**, e2033457, doi.org/10.1001/jamanetworkopen.2020.33457.
29. Firman C & Batterham RL (2022) A new era in gut hormone-based pharmacotherapy for people with obesity. *Proc Nutr Soc* **81**, 217–226.
30. Ludwig DS, Aronne LJ, Astrup A *et al.* (2021) The carbohydrate-insulin model: a physiological perspective on the obesity pandemic. *Am J Clin Nutr* **114**, 1873–1885.
31. Hall KD, Farooqi IS, Friedman JM *et al.* (2022) The energy balance model of obesity: beyond calories in, calories out. *Am J Clin Nutr* **115**, 1243–1254.
32. Speakman JR & Hall KD (2021) Carbohydrates, insulin, and obesity. *Science* **372**, 577–578.
33. Churuangsuk C, Hall J, Reynolds A *et al.* (2022) Diets for weight management in adults with type 2 diabetes: an umbrella review of published meta-analyses and systematic review of trials of diets for diabetes remission. *Diabetologia* **65**, 14–36.
34. Naude CE, Brand A, Schoonees A *et al.* (2022) Low-carbohydrate versus balanced-carbohydrate diets for reducing weight and cardiovascular risk. *Cochrane Database of Syst Rev* **1**, 1–456, doi.org/10.1002/14651858.CD013334.pub2.
35. Schutz Y, Montani J-P & Dulloo AG (2021) Low-carbohydrate ketogenic diets in body weight control: a recurrent plaguing issue of fad diets. *Obes Rev* **22**(Suppl. 2), e13195, doi.org/10.1111/obr.13195.
36. Jamshed H, Steger FL, Bryan DR *et al.* (2022) Effectiveness of early time-restricted eating for weight loss, fat loss, and cardiometabolic health in adults with obesity. A randomised clinical trial. *JAMA Intern Med* **182**, 953–962.
37. Liu D, Huang Y, Huang C *et al.* (2022) Calorie restriction with or without time-restricted eating in weight loss. *N Engl J Med* **386**, 1495–1504.
38. Paar EB, Devlin BL & Hawley JA (2022) Perspective: time-restricted eating – integrating the what with the when. *Adv Nutr* **13**, 699–711.
39. Luke A & Cooper RS (2013) Physical activity does not influence obesity risk: time to clarify the public health message. *Int J Epidemiol* **42**, 1831–1836.
40. Malhotra A, Noakes T & Phinney S (2015) It is time to bust the myth of physical inactivity and obesity: you cannot outrun a bad diet. *Br J Sports Med* **49**, 967–968.
41. King J (2022) Obesity. In *Physical Activity and Health: The Evidence Explained*, 3rd ed., pp. 196–239 [DJ Stensel, AE Hardman & JMR Gill, editors]. Oxon and New York: Routledge.
42. Archer E, Shook RP, Thomas DM *et al.* (2013) 45-Year trends in women's use of time and household management energy expenditure. *PLoS ONE* **8**, e56620, doi.org/10.1371/journal.pone.0056620.
43. Church TS, Thomas DM, Tudor-Locke C *et al.* (2011) Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. *PLoS ONE* **6**, e19657, doi.org/10.1371/journal.pone.0019657.
44. Healy GN, Matthews CE, Dunstan DW *et al.* (2011) Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–2006. *Eur Heart J* **32**, 590–597.
45. Hamann V, Deruelle P, Enaux C *et al.* (2022) Physical activity and gestational weight gain: a systematic review of observational studies. *BMC Public Health* **22**, 1951, doi.org/10.1186/s12889-022-14324-0.
46. Kujala UM, Leskinen T, Rottensteiner M *et al.* (2022) Physical activity and health: findings from Finnish monozygotic twin pairs discordant for physical activity. *Scand J Med Sci Sports* **32**, 1316–1323.
47. Levine JA, Lanningham-Foster LM, McCrady SK *et al.* (2005) Interindividual variation in posture allocation: possible role in human obesity. *Science* **307**, 584–586.
48. Pontzer H, Raichlen DA, Wood BM *et al.* (2012) Hunter gatherer energetics and human obesity. *PLoS ONE* **7**, e40503, doi.org/10.1371/journal.pone.0040503.
49. Pontzer H, Raichlen DA, Gordon AD *et al.* (2014) Primate energy expenditure and life history. *Proc Natl Acad Sci* **111**, 1433–1437.
50. Pontzer H (2015) Constrained total energy expenditure and the evolutionary biology of energy balance. *Exerc Sport Sci Rev* **43**, 110–116.
51. Pontzer H, Brown MH, Raichlen DA *et al.* (2016) Metabolic acceleration and the evolution of human brain size and life history. *Nature* **533**, 390–392.
52. Pontzer H, Durazo-Arvizu R, Dugas LR *et al.* (2016) Constrained total energy expenditure and metabolic adaptation to physical activity in adult humans. *Curr Biol* **26**, 410–417.
53. Careau V, Halsey LG, Pontzer H *et al.* (2021) Energy compensation and adiposity in humans. *Curr Biol* **31**, 4659–4666.
54. Rimbach R, Yamada Y, Sayagama H *et al.* (2022) Total energy expenditure is repeatable in adults but not associated with short-term changes in body composition. *Nat Commun* **13**, 99, doi.org/10.1038/s41467-021-27246-z.
55. Ross R, Dagnone D, Jones PJH *et al.* (2000) Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. *Ann Intern Med* **133**, 92–103.
56. Ross R, Freeman JA & Janssen I (2000) Exercise alone is an effective strategy for reducing obesity and related comorbidities. *Exerc Sport Sci Rev* **28**, 165–170.
57. Donnelly JE, Blair SN, Jakicic JM *et al.* (2009) Appropriate physical activity intervention strategies for weight loss and prevention of weight regain in adults. *Med Sci Sports Exerc* **41**, 459–471.

https://doi.org/10.1017/S0029665123002203 Published online by Cambridge University Press

58. Bellicha A, van Baak MA, Battista F *et al.* (2021) Effects of exercise training on weight loss, body composition changes, and weight maintenance in adults with overweight or obesity: an overview of 12 systematic reviews and 149 studies. *Obes Rev* **22**(Suppl. 4), e13256, doi.org/10.1111/obr.13256.
59. Dhurandhar EJ, Kaiser KA, Dawson JA *et al.* (2015) Predicting adult weight change in the real world: a systematic review and meta-analysis accounting for compensatory changes in energy intake or expenditure. *Int J Obes* **39**, 1181–1187.
60. Broskey NT, Martin CK, Burton JH *et al.* (2021) Effect of aerobic exercise-induced weight loss on the components of daily energy expenditure. *Med Sci Sports Exerc* **53**, 2164–2172.
61. Lund J, Gerhart-Hines Z & Clemmensen C (2020) Role of energy excretion in human body weight regulation. *Trends Endocrin Metab* **31**, 705–708.
62. Bouchard C, Tremblay A, Despres J-P *et al.* (1994) The response to exercise with constant energy intake in identical twins. *Obes Res* **2**, 400–410.
63. Thomas HJ, Marsh CE, Maslen BA *et al.* (2021) Studies of twin responses to understand exercise therapy (STRUETH): body composition. *Med Sci Sports Exerc* **53**, 58–67.
64. Barber JL, Ruiz-Ramie JJ, Robbins JM *et al.* (2021) Regular exercise and patterns of response across multiple cardiometabolic traits: the HERITAGE family study. *Br J Sports Med* **56**, 95–100.
65. Haganes KL, Silva CP, Eyjólfsdóttir SK *et al.* (2022) Time-restricted eating and exercise training improve HbA1c and body composition in women with overweight/obesity: a randomised controlled trial. *Cell Metab* **34**, 1457–1471.
66. Lundgren JR, Janus C, Jensen SBK *et al.* (2021) Healthy weight loss maintenance with exercise, liraglutide, or both combined. *N Engl J Med* **384**, 1719–1730.
67. Busetto L, Bettini S, Makaronidis J *et al.* (2021) Mechanisms of weight regain. *Eur J Intern Med* **93**, 3–7.
68. Butryn ML, Crane TN, Lufburrow E *et al.* (2022) The role of physical activity in long-term weight loss: 36-month results from a randomised controlled trial. *Ann Behav Med* **57**, 146–154.
69. Berthold H-R, Morrison CD, Ackroff K *et al.* (2021) Learning of food preferences: mechanisms and implications for obesity and metabolic diseases. *Int J Obes* **45**, 2156–2168.
70. Watts AG, Kanoski SE, Sanchez-Watts G *et al.* (2022) The physiological control of eating: signals, neurons, and networks. *Physiol Rev* **102**, 689–813.
71. Cunningham PM & Rolls BJ (2021) The satiation framework: exploring processes that contribute to satiation. *Physiol Behav* **236**, 113419, doi.org/10.1016/j.physbeh.2021.113419.
72. Azevedo EP, Ivan VJ, Friedman JM *et al.* (2022) Higher-order inputs involved in appetite control. *Biol Psychiatry* **91**, 869–878.
73. Deem JD, Faber CL & Morton GJ (2022) AgRP neurones: regulators of feeding, energy expenditure, and behaviour. *FEBS J* **289**, 2362–2381.
74. Theilade S, Christensen MB, Vilsbøll T *et al.* (2021) An overview of obesity mechanisms in humans: endocrine regulation of food intake, eating behaviour and common determinants of body weight. *Diabetes Obes Metab* **23** (Suppl. 1), 17–35.
75. Dorling J, Broom DR, Burns SF *et al.* (2018) Acute and chronic effects of exercise on appetite, energy intake, and appetite-related hormones: the modulating effect of adiposity, sex, and habitual physical activity. *Nutrients* **10**, 1140, doi: 10.3390/nu10091140.
76. Ouerghi N, Feki M, Bragazzi NL *et al.* (2021) Ghrelin response to acute and chronic exercise: insights and implications from a systematic review of the literature. *Sports Med* **51**, 2389–2410.
77. Ropelle ER, da Silva ASR, Cintra DE *et al.* (2021) Physical exercise: a versatile anti-inflammatory tool involved in the control of hypothalamic satiety signalling. *Exerc Immunol Rev* **27**, 7–23.
78. Douglas JA, King JA, Clayton DJ *et al.* (2017) Acute effects of exercise on appetite, *ad libitum* energy intake and appetite-regulatory hormones in lean and overweight/obese men and women. *Int J Obes* **41**, 1737–1744.
79. Chen Y-C, Walhin J-P, Hengist A *et al.* (2022) Interrupting prolonged sitting with intermittent walking increases postprandial gut hormone responses. *Med Sci Sports Exerc* **54**, 1183–1189.
80. Frampton J, Edinburgh RM, Ogden HB *et al.* (2022) The acute effect of fasted exercise on energy intake, energy expenditure, subjective hunger and gastrointestinal hormone release compared to fed exercise in healthy individuals: a systematic review and network meta-analysis. *Int J Obes* **46**, 255–268.
81. Goltz FR, Thackray AE, King JA *et al.* (2018) Interindividual responses of appetite to acute exercise: a replicated crossover study. *Med Sci Sports Exerc* **50**, 758–768.
82. Flack KD, Anderson RE, McFee KF *et al.* (2022) Exercise increases attentional bias towards food cues in individuals classified as overweight or obese. *Physiol Behav* **247**, 113711, doi.org/10.1016/j.physbeh.2022.113711.
83. King NA, Caudwell PP, Hopkins M *et al.* (2009) Dual-process action of exercise on appetite control: increase in orexigenic drive but improvement in meal-induced satiety. *Am J Clin Nutr* **90**, 921–927.
84. Stubbs RJ, Sepp A, Hughes DA *et al.* (2002) The effect of graded levels of exercise on energy intake and balance in free-living women. *Int J Obes* **26**, 866–869.
85. Stubbs RJ, Hughes DA, Johnstone AM *et al.* (2004) A decrease in physical activity affects appetite, energy, and nutrient balance in lean men feeding ad libitum. *Am J Clin Nutr* **79**, 62–69.
86. Beaulieu K, Blundell JE, van Baak MA *et al.* (2021) Effect of exercise training interventions on energy intake and appetite control in adults with overweight or obesity: a systematic review and meta-analysis. *Obes Rev* **22** (Suppl. 4), e13251, doi.org/10.1111/obr.13251.
87. Li VL, He Y, Contrepois K *et al.* (2022) An exercise-inducible metabolite that suppresses feeding and obesity. *Nature* **606**, 785–790.
88. Grannell A, Kokkinos A & le Roux CW (2022) Myokines in appetite control and energy balance. *Muscles* **1**, 26–47.
89. Klein AB, Kleinert M, Richter EA *et al.* (2022) GDF15 in appetite and exercise: essential player of coincidental bystander. *Endocrinology* **163**, 1–10, doi.org/10.1210/endocr/bqab242.
90. McCarthy SF, Islam H & Hazell TJ (2020) The emerging role of lactate as a mediator of exercise-induced appetite suppression. *Am J Physiol Endocrinol Metab* **319**, E814–E819.
91. Mavanji V, Pomonis B & Kotz CM (2021) Orexin, serotonin, and energy balance. *WIREs Mech Dis* **14**, e1536, doi.org/10.1002/wsbm.1536.
92. Jansson J-O, Palsdottir V, Hägg DA *et al.* (2021) Body weight homeostat that regulates fat mass independently

of leptin in rats and mice. *Proc Natl Acad Sci* **115**, 427–432.
93. Karra E, O'Daly OG, Choudhury AI *et al.* (2013) A link between FTO, ghrelin, and impaired brain food-cue responsivity. *J Clin Invest* **123**, 3539–3551.
94. Dorling JL, Clayton DJ, Jones J *et al.* (2019) A randomized crossover trial assessing the effects of acute exercise on appetite, circulating ghrelin concentrations, and butyrylcholinesterase activity in normal-weight males with variants of the obesity-linked FTO rs9939609 polymorphism. *Am J Clin Nutr* **110**, 1055–1066.
95. Hiraike Y, Yang C-T, Liu W-J *et al.* (2021) FTO obesity variant–exercise interaction on changes in body weight and BMI: the Taiwan Biobank study. *J Clin Endocrinol Metab* **106**, e3673–e3681.
96. Stensel DJ, Hardman AE & Gill JMR (editors) (2022) *Physical Activity and Health: The Evidence Explained*, 3rd ed. Oxon and New York: Routledge.
97. Hargreaves M (2021) Exercise and health: historical perspectives and new insights. *J Appl Physiol* **131**, 575–588.
98. Chow LS, Gerszten RE, Taylor JM *et al.* (2022) Exerkines in health, resilience and disease. *Nat Rev Endocrinol* **18**, 273–289.
99. Del Pozo Cruz B, Ahmadi MN, Lee I-M *et al.* (2022) Prospective associations of daily step counts and intensity with cancer and cardiovascular disease incidence and mortality and all-cause mortality. *JAMA Intern Med* **182**, 1139–1148.
100. Paluch AE, Gabriel KP, Fulton JE *et al.* (2021) Steps per day and all-cause mortality in middle-aged adults in the coronary artery risk development in young adults study. *JAMA Netw Open* **4**, e2124516, doi.org/10.1001/jamanetworkopen.2021.24516.
101. Saint-Maurice PF, Graubard BI, Troiano RP *et al.* (2022) Estimated number of deaths prevented through increased physical activity among US adults. *JAMA Intern Med* **182**, 349–352.
102. Master H, Annis J, Huang S *et al.* (2022) Association of step counts over time with the risk of chronic disease in the *All of Us* research program. *Nat Med* **28**, 2301–2308.
103. Li S, Lear SA, Rangarajan S *et al.* (2022) Association of sitting time with mortality and cardiovascular events in high-income, middle-income, and low-income countries. *JAMA Cardiol* **7**, 796–807.
104. Rizzuto D, Orsini N, Qiu C *et al.* (2012) Lifestyle, social factors, and survival after age 75: population based study. *Br Med J* **345**, e5568, doi.org/10.1136/bmj.e5568.
105. Lee I-M, Shiroma EJ, Lobelo F *et al.* (2012) Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* **380**, 219–229.
106. Erickson KI, Voss MW, Prakash RS *et al.* (2011) Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci* **108**, 3017–3022.
107. Dhana K, Franco OH, Ritz EM *et al.* (2022) Healthy lifestyle and life expectancy with and without Alzheimer's disease dementia: population based cohort study. *Br Med J* **377**, e068390, doi.org/10.1136/bmj-2021-068390.
108. Del Pozo Cruz B, Ahmadi M, Naismith SL *et al.* (2022) Association of daily step count and intensity with incident dementia in 78,430 adults living in the UK. *JAMA Neurol* **79**, 1059–1063.
109. Pontzer H, Yamada Y, Sagayama H *et al.* (2021) Daily energy expenditure through the human life course. *Science* **373**, 808–812.
110. Rhoads TW & Anderson RM (2021) Taking the long view on metabolism. *Science* **373**, 738–739.
111. Ahern AL, Breeze P, Fusco F *et al.* (2022) Effectiveness and cost-effectiveness of referral to a commercial open group weight management programme in adults with overweight and obesity: 5-year follow-up of the WRAP randomised controlled trial. *Lancet Public Health* **7**, e866–e875, doi.org/10.1016/S2468-2667(22)00226-2.
112. Hartmann-Boyce J, Theodoulou A, Oke JL *et al.* (2021) Association between characteristics of behavioural weight loss programmes and weight change after programme end: systematic review and meta-analysis. *Br Med J* **374**, 1–10, doi.org/10.1136/bmj.n1840.
113. Gaesser GA & Angadi SS (2021) Obesity treatment: weight loss versus increasing fitness and physical activity for reducing health risks. *iScience* **24**, 102995, doi.org/10.1016/j.isci.2021·102995.
114. Davies MJ, Aroda VR, Collins BS *et al.* (2022) Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **45**, 2753–2786.
115. Pearce M, Garcia L, Abbas A *et al.* (2022) Association between physical activity and risk of depression. A systematic review and meta-analysis. *JAMA Psychiatry* **79**, 550–559.
116. Tasali E, Wroblewski K, Kahn E *et al.* (2022) Effect of sleep extension on objectively assessed energy intake among adults with overweight in real-life settings. A randomized clinical trial. *JAMA Intern Med* **182**, 365–374.
117. Gao M, Piernas C, Astbury NM *et al.* (2021) Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. *Lancet Diabetes Endocrinol* **9**, 350–359.
118. Sallis R, Young DR, Tartof SY *et al.* (2021) Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48,440 adult patients. *Br J Sports Med* **55**, 1099–1105.
119. Dietz WH & Pryor S (2022) How can we act to mitigate the global syndemic of obesity, undernutrition, and climate change? *Curr Obes Rep* **11**, 61–69.

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