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**Title:**

The role of physical activity in the regulation of body weight: The overlooked contribution of light physical activity and sedentary behaviors

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33    **Conflicts of interest**

34    The authors have no conflicts of interest to declare.

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36     **Abbreviations**

- 37     PA: physical activity
- 38     MVPA: moderate-to-vigorous physical activity
- 39     LPA: light physical activity
- 40     SB: sedentary behaviors
- 41     BM: body mass
- 42     EE: energy expenditure
- 43     TDEE: total daily energy expenditure
- 44     EI: energy intake
- 45     PAL: physical activity level
- 46     MET: metabolic equivalent
- 47     WHO: World Health Organization
- 48     NWCR: National Weight Control Registry

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**Abstract**

(192 /200 words)

The role of physical activity (PA) in the regulation of body weight is still a major topic of debate. This may be because studies have essentially focused on the effects of moderate/vigorous PA (or MVPA) on body weight while overlooking the other components of PA, namely light-intensity PA (LPA, daily life activities) and sedentary behaviors (SB, too much sitting). In this review, we will (i) describe the history of changes in PA behaviors that occurred with modernization, (ii) review data from cross-sectional and longitudinal studies that examined the associations between PA, SB and measures of obesity, (iii) review interventional studies that investigated the effects of changes in PA and SB on body weight and adiposity, and (iv) discuss experimental studies that addressed potential biological mechanisms underlying the effects of PA and SB on weight regulation. Overall recent findings support the importance of considering all components of PA to better understand the regulation of energy balance and suggest an important role for LPA and SB in addition to MVPA on body weight regulation. Longitudinal large-scale rigorous studies are needed to advance our knowledge of the role of PA/SB in combating the obesity epidemic.

## 66 Introduction

67 Although obesity is a complex multifactorial disease, weight gain can only result from chronic positive  
68 energy balance, *i.e.*, calorie consumption greater than energy needs. The causes of this imbalance  
69 however remain unclear. Over the past few years, a debate has been growing in the scientific community  
70 and the media on the relative contribution of increased energy intake (EI) vs reduced energy expenditure  
71 (EE) to the obesity epidemic. While the importance of physical activity (PA) in weight management is  
72 generally accepted, the role of PA in weight gain is more controversial<sup>1-7</sup>. Some investigators promote  
73 a diet-centric view according to which the global obesity epidemic observed over the past decades is  
74 due to increases in EI rather than to declines in EE due to a fall in habitual levels of PA. Alternatively,  
75 Rowland proposed the “activity-stat” concept in 1998<sup>8</sup> in which total daily EE (TDEE) is  
76 homeostatically regulated, *i.e.*, controlled around a fixed value. Pontzer et al.<sup>9</sup> recently proposed that  
77 TDEE is rather constrained. According to this theory, while EE increases with PA at low activity levels,  
78 it plateaus at higher activity levels as the body adapts to maintain TDEE within a narrow range. High  
79 activity levels may be offset by decreases in the other components of TDEE including resting metabolic  
80 rate (the minimal amount of energy required to ensure vital functions) and diet-induced thermogenesis  
81 (the energy required to assimilate and store energy after a meal). This model has been used to explain  
82 why increased levels of PA often have little impact on weight-loss strategies (about 1-2kg)<sup>10</sup>. While the  
83 role of PA in the treatment of obesity is controversial, its benefits for preventing unhealthy weight gain  
84 and body weight regain following weight loss is more generally accepted<sup>11</sup>.

85 Our research group subscribes to the view that the constrained TDEE model is not necessarily  
86 incompatible with a key role of PA in body weight and composition management. The plateau has been  
87 observed at PA levels (PAL, defined as the ratio between TDEE and resting metabolic rate) of about  
88 2.5-3.0, which are levels observed in professional athletes and competitors<sup>12</sup>, not in the general  
89 population whose PAL values are between 1.4-1.8<sup>13,14</sup>. Maintaining PAL values around 1.7-1.8 has been  
90 estimated to be enough to prevent body weight gain and regain after weight loss<sup>14-16</sup>. These observations  
91 support a role for PA in body weight regulation in the range of PALs observed in the general population.

In addition, research has tended to overlook the contribution of non-exercise activities (mainly composed of light intensity physical activities – LPA, *i.e.*, PA associated with metabolic equivalents – METs comprised between 1.6 and 2.9<sup>17</sup>), which correspond to activities of everyday life and any body movement, such as walking, taking the stairs, gardening<sup>18,19</sup> or activities other than volitional structured exercise<sup>20,21</sup>. These non-exercise activities are known to account for a large component of EE even in sedentary individuals. In addition, time spent in LPA is negatively, but tightly, associated with time spent in sedentary behaviors (SB)<sup>22</sup>. As trivial as it sounds, the more a person moves, the less time he/she spends in sedentary activities.

Research on SB has gained increasing attention over the past 10 years, especially with the development of activity monitors that allow to specifically measure this behavior. While the terms physical inactivity and SB are used interchangeably<sup>23,24</sup>, they are fundamentally different. Physical inactivity is defined as engaging in less PA than necessary to meet current public health guidelines, *i.e.*, 150-300 min of moderate to vigorous or 75-150 min of vigorous PA or an equivalent combination of moderate-to-vigorous PA (MVPA, PA characterized by an EE > 3 METs)<sup>17,25</sup>. By contrast, SB are defined as “any waking behavior characterized by an EE ≤ 1.5 METs, while in a sitting, reclining or lying posture” based on the terminology consensus of the Sedentary Behaviors Research Network (SBRN)<sup>26</sup>. Based on these definitions, an individual can paradoxically be both physically active and sedentary (**Figure 1**). Despite the wide promotion of PA recommendations, most people engage in high amounts of sedentary activities, *i.e.*, more than 55% of awake time<sup>27</sup>. In a meta-analysis regrouping 1 million men and women, Ekelund et al.<sup>28</sup> estimated that high levels of PA seem to be necessary to eliminate the increased risk of death induced by more than 8 hours per day spent in SB, a duration commonly observed in office workers<sup>29</sup>. Despite the associations between SB and chronic diseases<sup>30</sup>, there is a surprising lack of information on the roles that SB and physical inactivity play in the increasing prevalence of obesity.

- Please insert figure 1 near here -

The objective of this review is to summarize available data to discuss the role of PA in the obesity epidemic in adults, with a specific focus on SB and non-exercise LPA. We specifically (i) describe the changes in PA behaviors that have occurred over the past millennia, (ii) review data from cross-sectional and longitudinal studies that examined the associations between PA, SB and measures of obesity, (iii) review the interventional studies that investigated the effects of changes in PA and SB on obesity markers, and (iv) discuss the experimental studies that addressed some of the potential biological mechanisms underlying the effects of PA and SB on weight regulation. Although this is not a systematic review, we did our best to provide an unbiased and balanced perspective by presenting key findings currently available to inform the debate on the role of PA/SB in body weight regulation.

**1. Historical changes in habitual physical activity patterns**

**1.1. Physical activity patterns from ancient times to the present**

Current human physiology and behavior are the result of natural selection in *Homo Sapiens* who emerged about 200,000 years ago. In the Paleolithic era (approx. 40-50,000 years ago), our ancestors hunted and gathered food. These activities required sustained activities at high levels of EE for 1-2 hours/day. Moreover, inactive periods were probably composed of squatting, kneeling or otherwise sitting in postures that required continuous very low to low intensity muscle activity limiting the deleterious effects of sedentariness that are observed in current industrialized populations<sup>31</sup>. With the development of agriculture (approx. 10,000 years ago), humans needed to perform moderate intensity activities for 6-8 hours/day<sup>32</sup>. The former “intermittently active” lifestyle corresponding to cycles of short bouts of intense activities alternating with long resting periods was replaced by continuous and sustained bouts of moderate intensity activity that were necessary to perform agricultural tasks without the benefit of modern technology. Lightfoot<sup>32</sup> estimated that non-technological agricultural activity required 3-5 fold more active time than hunting/gathering. Although activity-related EE was similar



between both pre-industrial populations, it was significantly higher than what has been measured in modern westernized populations<sup>32</sup>.

While PA pattern progressively changed over several millennia, rapid and major changes have occurred over the past 200 years. Since the Industrial Revolution (end of the 19<sup>th</sup> century in the United Kingdom), and more recently with the Great Acceleration (second half of the 20<sup>th</sup> century), industrial, technological and digital advances have resulted in societal and behavioral changes in PA habits<sup>33</sup>. The former "traditional" environment, characterized by relatively scarce food and high EE, gave way to the modern "social" and "built" environment that promotes obesogenic behaviors. Today, being physically inactive does not jeopardize access to food due to the abundance of low-cost, high-fat, energy-dense food<sup>32</sup>. These changes in habitual PA pattern are however not uniform worldwide<sup>34</sup>. The prevalence of physical inactivity is negatively associated with the Human Development Index (HDI, a statistic composite index of life expectancy, education, and per capita income, used to rank countries into four tiers of human development)<sup>35,36</sup>. Populations living in countries associated with the lowest HDI quartile have a significantly lower prevalence of physical inactivity than those in the highest quartile. Populations that have completed the epidemiological transition (*i.e.*, shift in the causes of death from deaths due to high children mortality and infectious diseases to deaths due to lifestyle-related and chronic diseases) along with their nutritional and physical activity transitions are particularly vulnerable to physically inactive and sedentary lifestyles<sup>37</sup>.

## 1.2. Modern life: Widespread adoption of sedentary and physically inactive lifestyles

In westernized populations, industrial and technological revolutions have engineered PA out of virtually every facet of daily life, *i.e.*, occupational (desk-bound jobs), domestic (dishwashers, washing machines), transport (cars) and leisure activities (video games, the internet, television.)<sup>38</sup>. Based on body temperature measurement, Yegian et al.<sup>39</sup> estimated that MVPA decreased by 27 min per day since 1820 in the U.S. By contrast, the global prevalence of physically inactive people has risen from 20% to 27.5%

between 2011 and 2016, and keeps increasing<sup>40</sup>. These data based on self-reported population-based surveys likely overestimate PA<sup>41</sup>. For example, while 51% of the U.S. population self-reported reaching recommended levels of PA in the National Health and Nutrition Examination Survey (NHANES study, 2003-2004), only 5% of individuals actually achieved these levels when data were objectively collected with an accelerometer<sup>42</sup>.

Along with this reduction in PA, time spent in sedentary activities has increased in every sphere of daily life. For example, time spent watching TV has increased by 61.4% in U.S. adults between 1950 and 2000 reaching up to 8 hours per day<sup>43</sup>. By contrast, the time children and adolescents spend watching TV decreased by approximatively 23% between 1981 and 1997. This was associated with a concomitant decrease in free-time by 12% mostly explained by an increased time away from home, primarily in school, day care, and after-school programs<sup>44</sup>. Nowadays, 86% of workers have sedentary jobs, spending 66% of their total work time sitting<sup>45</sup>, with a reciprocal reduction in physically active tasks. The expansion of the service sector of the economy has reduced time spent physically active in the workplace by 32% since 1960. A further drop of 45% is expected by 2030 in the U.S. and a reduction from 19% to 35% in the United Kingdom<sup>46</sup>. Although physical inactivity (*i.e.*, not reaching current public health guidelines) has not further increased in U.S. adults between 2001 and 2016<sup>40</sup>, self-reported daily time spent in SB (*i.e.*, too much sitting) increased from 5.7 hours in 2007-2008 to 6.4 hours in 2015-2016<sup>47</sup>. Accelerometry-derived data reported more than 8 daily hours spent in SB with an average of 8.2 daily hours in the U.S.<sup>48</sup> and 8.8 hours in Europe<sup>49</sup>. Thus, these changes in PA/SB have the potential to impact TDEE and increase the risks of ill effects of SB.

### 1.3. Consequences of the reduction of habitual physical activity on total daily energy expenditure

Several studies have tried to assess changes in TDEE over time. Measured EE of modern societies were compared to either the estimated EE of our ancestors or to the measured EE of modern populations who have maintained a pre-industrial lifestyle. Cordain et al.<sup>50</sup> estimated that TDEE of modern humans is

about 65% of the TDEE of people living in the late Paleolithic Stone Age. Based on this estimate, they wrote that our modern PAL is “below the level of physical exertion for which our genetically-determined physiology and biochemistry have been programmed through evolution”. The same research group further showed that modern hunter-gatherers had higher levels of PA than individuals living in the modern U.S. They estimated that the difference was equivalent to walking 19 km per day for an adult of 70kg, or 1,190 kcal/day<sup>50</sup>. Leonard<sup>51</sup> estimated that PAL was significantly lower in industrial as compared to modern subsistence populations, reflecting a less active way of life. He calculated that individuals living a subsistence lifestyle expended 411 kcal/day more than those living a modern lifestyle. By comparison, following the American College of Sports Medicine (ACSM) PA recommendations accounts for only 69 kcal/day, and 1 daily hour of intense exercise accounts for 330 kcal/day<sup>52</sup>. Egger et al.<sup>53</sup> compared EE in a group of actors paid to live like early Australian settlers to that of a group of modern sedentary office workers. He estimated that activity levels were on average 1.6-fold lower in industrialized population than that of the forefathers from 150 years earlier. This was equivalent to a difference of 8km/day of walking or about 380 kcal/day for a 70kg male.

Between 1950 and 2000, occupations associated with low intensity PA increased by more than 80% while those requiring high intensity PA declined by 25%<sup>43</sup>. It has been estimated that these changes resulted in a decrease in work related EE of 130 kcal/day over 50 years<sup>54</sup>. Some studies suggest this drop in occupational PA was offset by an increase in PA during leisure time<sup>43</sup>. However, other studies found that leisure PA only increased by 0.5% per year in Australian males between 1989 and 2011<sup>55</sup>. It was also estimated that leisure-time PA slightly increased in U.S. adults between the 1990’s and the 2000’s associated with a substantial decline in household, work and transport-related activities<sup>43</sup>. Although informative, all these data have to be taken with caution given they were self-reported. It is only from the 2000’s that the objective measurement of daily PA patterns has become common with the development and growing availability of reliable activity monitors<sup>56</sup>.

Taken together, these studies suggest that there has been a major drop in PA over the millennia with a hypothetical average EE about 400-1,100 kcal/day greater in early *Homo Sapiens* compared to the modern “*Homo Sedentarius*” who suffers from “diseases of civilization”<sup>32</sup> (**Figure 2**). Decreases in PA and PA-related EE in high income societies have been reported in more recent years, from the 1950s-1970s. On the other hand, data from NHANES showed an increase in EI of 168 and 335 kcal/day for men and women, respectively between 1970 and 2000<sup>57</sup>. These changes in PA and EI happened at a time when the prevalence of obesity increased in the early 1980’s in the U.S. and Western Europe<sup>58</sup>. Of note, the chronic energy imbalance, or energy gap, (*i.e.*, difference between EI and EE) thought to be at the origin of the obesity epidemic in the U.S. is only about 50-100 kcal/day<sup>59</sup>. Although a parallel can be made between the transition in PA and the global rise in overweight and obesity prevalence, some objective data do not necessarily support a decline in TDEE over the past decades. When combining data using gold standard doubly labelled water (DLW)-derived TDEE collected between the 1980’s and early 2000’s, Westerterp & Speakman did not find any change in total or activity-related EE<sup>60</sup>. These observations and others have fed the debate on the role of PA in weight gain and its role in the obesity epidemic. However, it is possible that changes in PA and TDEE or activity-related EE occurred before the 1980’s. The impact of the changes in PA over time on TDEE therefore remains an open question. Relationships between PA, SB and epidemiological measures of obesity can however bring valuable insight on the influence of low levels of PA on body weight regulation (**Box 1**).

- Please insert box 1 and figure 2 near here -

## 2. Associations between physical activity, sedentariness and measures of obesity prevalence

### 2.1. Associations from cross-sectional population studies

Most, but not all cross-sectional studies have reported negative associations between PAL and measures of obesity including body weight, body mass index (BMI), waist circumference and adiposity in adults but also in adolescents and children<sup>61-65</sup>. For example, data on almost 3,000 children and adolescents

assessed in the NHANES study showed that the least active group had the highest trunk fat mass<sup>66</sup>. Drenowatz et al.<sup>67</sup> observed in 430 adults (average age 27.7 y.o.) that the proportion of energy expended in MVPA is lower in people with overweight than in those with normal weight. On a larger scale, Füzéki et al.<sup>68</sup> reviewed the health benefits of LPA from the NHANES accelerometer dataset and included a total of 37 studies conducted in adults (16 studies in a general adult population, 14 in adults with chronic diseases, 9 in older adults and 1 in pregnant women). Eight studies showed negative associations between time spent in LPA and waist circumference and four also reported negative associations with BMI. A fifth study observed a negative association between LPA and waist circumference, but not with BMI. The authors concluded that inactive people should engage in PA of any intensity, the duration of the bouts being more important than intensity to protect against weight gain<sup>68</sup>. A recent review from Jakicic et al.<sup>69</sup> summarizing results from cross-sectional studies conducted in adults with overweight and obesity concluded that BMI was inversely associated with total volume of MVPA when MVPA was accumulated in bouts lasting more than 10 min. These data while suggestive of a relationship between PA and obesity, do not allow definitive conclusions to be drawn.

Only a few studies have examined the associations between time spent in SB and body weight. Anjana et al.<sup>70</sup> reported a negative relationship between self-reported sitting time and BMI and waist circumference in 543 Indian adults. Martínez-González et al.<sup>71</sup> conducted a survey in 15,239 men and women >15 years of age living in the 15 member states of the European Union in 1999. They observed independent associations between leisure-time PA, sitting time and body mass. More importantly, sedentary time was positively associated with trunk fat, independent of time spent in MVPA. Observational studies report that people who are overweight spend in general 2.5 hours/day sitting more than people with normal weight, and they engage in bouts of SB that are of longer duration<sup>30,72</sup>. Conversely, people with normal weight interrupt prolonged sedentary periods with short bouts of PA more often and spend more time in LPA than people who are overweight<sup>22</sup>.

Altogether these cross-sectional population studies show that people who are less active especially when engaging in active bouts of less than 10 min, and who spend more time in sedentary activities are more

likely to have higher body weight, BMI, adiposity and waist circumference. In contrast, active bouts longer than 10 min, independent of the intensity (*i.e.*, LPA or MVPA), are positively associated with less obesity<sup>69</sup>. However, a correlation does not necessarily indicate causality. Do people with overweight or obesity sit more and are less active because of the higher energy cost of moving their heavier body, or do they weigh more because they sit more and are less active? The fact that habitual exercisers are leaner than their inactive counterparts limits the interpretation of causality between PA and body weight and composition. Potential confounding variables such as diet, habitual PA or maximal aerobic capacity have also rarely been taken into account in these studies. Although observational and epidemiological studies are informative, longitudinal studies provide better evidence regarding causality, and long-term prospective randomized controlled trials (RCT) provide the best evidence on the relationships between PA and weight.

## 2.2. Associations from longitudinal studies

A large number of studies has shown that people who are the most active gain the least weight over time. In 2018, the Physical Activity Guidelines Advisory Committee<sup>73</sup> identified in a literature review 40 studies that assessed the relationship between PA and weight gain in adults over a follow-up period ranging from 1 to 22 years. The authors reported strong evidence supporting relationships between greater amounts of MVPA and attenuated weight gain in adults. A lack of long-term studies however limited evidence to support a dose-response relationship with LPA. Observational studies also report strong relationships between PA and prevention of long-term weight regain following weight loss. The National Weight Control Registry (NWCR) is the largest prospective investigation of long-term successful weight loss maintenance<sup>74-76</sup> in more than 10,000 people who have lost at least 13.6 kg and have kept the weight off for at least one year. Studies from the registry have shown that people who have been successful with weight loss maintenance were people who maintain low EI and performed high levels of PA<sup>77</sup>. Most participants in the NWCR regularly engaged in structured PA<sup>74-76</sup> and self-reported one hour per day of MVPA<sup>76</sup>, which exceeds the World Health Organization (WHO) physical

activity guidelines for adults. Altogether data from the NWCR support a key role for PA in weight loss maintenance.

More recently, longitudinal studies have examined associations between sedentariness and weight status. The CARDIA study<sup>78</sup> conducted in 1,826 adults (average age 45.4 y.o.) with overweight or obesity observed that total and prolonged bouts of sedentary time ( $\geq 10$  min) were directly associated with BMI and waist circumference at baseline. After 5-year of follow-up, only prolonged sedentary bouts at baseline, not total daily sedentary time, were associated with greater gain in BMI and waist circumference<sup>78</sup>. Results from the Nurses' Health Study cohort (1992-1998)<sup>79</sup> collected in 68,487 women aged between 30 and 55 y.o. showed that each additional 2 hours per day spent in TV viewing increased obesity risk by 23% after a 6-year follow-up. Campbell et al.<sup>80</sup> conducted a meta-analysis on 23 prospective cohort studies in adults  $>18$  y.o. from North America and Europe (follow-up ranging from 1 to 21 years). They observed that the most sedentary individuals at baseline had a 1.33-fold higher risk of developing overweight or obesity compared with the least sedentary individuals (mean difference of 8 hours/day in SB between both groups). They estimated that an increment of 1 hour/day in SB was associated with a significant (but not clinically relevant) 0.02 cm increase in waist circumference over 5 years. Nevertheless, the authors found inconsistent and non-significant associations between SB at baseline and other measures of obesity due to a high degree of heterogeneity in the data. Twenty one studies out of the 23 included in this review used questionnaires to assess SB, which are known to overestimate PA and underestimate SB<sup>41,81</sup>; while only two used accelerometry-derived data for assessing daily time spent in SB. To identify the determinants of longitudinal weight gain, a recent clinical trial examined associations between metabolic and behavioral responses to short-term overfeeding and 5-year changes in body mass and composition in adults with normal weight. Individuals who reduced their objectively measured sedentary time the least following a 3-day overfeeding period were those who gained the most body and fat mass over 5 years of observation. Of note, no association was observed between the changes in total calorie intake, TDEE, or daily time spent in MVPA and LPA

in response to the acute overnutrition and longitudinal weight gain<sup>82</sup>. This finding supports a role for SB in the regulation of body weight and adiposity.

In summary, studies tend to support the idea that greater time spent in SB is associated with weight gain and obesity. But contrary to the consistent associations with MVPA supporting a preventive effect of PA against longitudinal weight gain and regain, there is a lack of prospective large-scale studies and rigorous data to make clear conclusions on the influence of SB on weight changes over time.

### 2.3. Interventional studies

#### *2.3.1. Effect of changes in physical activity and sedentary behaviors on the prevention of unhealthy weight gain*

The French ICAPS (Intervention Centered on Adolescents' Physical activity and Sedentary behavior) study<sup>83</sup> aimed to both increase PA and reduce SB in 954 students (aged 11-12). This landmark socio-ecological study relied upon a 4-year multi-level intervention that targeted the physical, organizational (school, city) and social (teachers, peers, families) living environment of the children and the children themselves through the synergistic actions of multiple partners. Compared to the control schools (no intervention), pupils who received the intervention increased time spent in PA (-0.05 vs +0.90 hours/week, respectively), decreased sedentary time (-4.7 vs -19.9 min/day TV/video viewing, respectively) and gained less weight throughout the 4 year-study (+0.41 kg/m<sup>2</sup> vs +0.10 kg/m<sup>2</sup> excess BMI, respectively)<sup>84</sup>. Importantly, the lifestyle changes induced by the intervention and the prevention of weight gain were maintained 2.6 years after the end of the intervention with the highest efficacy in the most sedentary and poorest adolescents<sup>84</sup>. In a similar manner, the Dutch FATaintPHAT protocol<sup>85</sup> aimed to assess the efficacy of a computer-tailored program for adolescent students (aged 12-13) targeting energy balance-related behaviors (*i.e.*, food intake and PA/SB). This 4-month cluster-randomized trial included 20 schools with a 2-year follow-up. The intervention contributed to develop knowledge on risk behaviors and favored intention towards changing these behaviors. The intervention



resulted in lower BMI and waist circumference at 2-years of follow-up in adolescents in the treatment arm compared to those in the control group<sup>85</sup>. The French ICAPS and the Dutch FATaintPHAT both strongly support a role for SB reduction along with an increase in PA for preventing longitudinal weight gain in children and adolescents. To our knowledge, no similar longitudinal study exists in adults or elderly. Robust data from such studies are needed to support the role of PA in the primary prevention of unhealthy weight in adults.

**- Please insert box 2 near here -**

### *2.3.2. Effect of changes in physical activity and sedentary behaviors on weight loss*

A general consensus is that exercise training (*i.e.*, MVPA) triggers physiological and behavioral compensatory mechanisms that counteract the exercise-induced energy deficit and lead to only a modest weight loss (1-2kg)<sup>10</sup>. Exercise training is therefore generally not considered to be an effective tool to produce weight loss. Yet, clinically relevant weight loss can be achieved if training is above PA recommendations, daily practiced and/or performed under supervision<sup>86-88</sup>. In the Midwest Exercise Trial (MET) 2 study<sup>89,90</sup>, adults with overweight or obesity lost on average 5% of their initial body weight following a 10-month training with an expenditure of 400-600 kcal per supervised exercise session 5 times a week. Nevertheless, high inter-individual variability was observed. Interestingly, those who lost weight (*i.e.*, responders, >5% body weight loss) spontaneously decreased time spent in SB during the 10-month intervention in favor of an increase in non-exercise PA (-27 min and + 39 min, respectively); no change was observed in the daily PA pattern of non-responders (<5% initial body weight). The E-MECHANIC study<sup>91</sup> further showed that low levels of habitual MVPA and activity-related EE are associated with less weight loss during a 24-week exercise intervention in adults with overweight or obesity. In the Step-Up study<sup>92</sup>, an 18-month behavioral weight loss intervention that combined calorie restriction and PA in adults with overweight or obesity (aged 18-55) the individuals who lost more than 10% of initial body weight spent more time in prolonged bouts (>10 min) of both

MVPA and LPA. Secondary analyses of large intervention studies in adults with overweight or obesity involved in the Diabetes Prevention Program (DPP) or Look AHEAD study also suggested that decreasing SB, particularly of long duration and replacing sedentary time with MVPA, is associated with weight loss<sup>93</sup>. Furthermore, while interventions based on low volumes of exercise training did not produce much weight loss<sup>94-96</sup>, training above the current PA recommendations (225-420 min/week of exercise or MVPA) have shown more success<sup>97</sup>. However, other studies showed that high volume of additional PA can induce concomitant decreases in non-exercise PA and increases in SB, especially in people with overweight or obesity<sup>98-100</sup> and low levels of habitual PA<sup>91</sup>. The factors triggering the spontaneous behavioral compensations and the associated inter-individual variability are however still unclear.

The commonly observed compensatory decreases in LPA in response to high volumes of MVPA may result from the difficulty that sedentary-inactive people encounter when performing unusual and/or new activities of moderate-to vigorous intensity. For those individuals, increasing LPA may be a reasonable alternative to increase total PA time<sup>101</sup>. Because LPA represents the most variable component of TDEE<sup>102</sup>, it has the potential to influence energy balance and hence, body weight. For example, the study from Holliday et al.<sup>21</sup> compared the effect of two interventions: one targeting LPA through increases in daily PA and another targeting MVPA (5 sessions per week of 30 min/day). The first intervention promoting participation in daily life activities resulted in higher daily time spent in LPA, lower sedentary time and greater android fat loss after 24 weeks compared to what was observed in the group assigned to the structured MVPA program. Of note, while the time spent in PA of different activities varied between the two groups at the end of the intervention, the total daily active time was not different. This study supports the promotion of activities of daily living as an efficient strategy to increase total PA, reduce body mass and improve adiposity. More recently, Swift et al.<sup>103</sup> observed that the combination of an aerobic exercise protocol with increases in daily steps (to avoid sedentariness) in adults with obesity was more effective than a protocol based on aerobic exercise alone in decreasing waist circumference (-4.7 vs -2.1 cm, respectively), body weight (-4.1kg or -3.5% vs -1.7kg or -1.8%,

respectively) and fat mass (-4.7 vs -2.6%). Based on these current findings, promoting LPA to decrease sedentariness can be considered a promising strategy to promote weight loss in physically inactive people with overweight or obesity.

Another approach is to target SB in addition to PA<sup>104,105</sup>. Fanning et al.<sup>106</sup> conducted a study of adding structured aerobic exercise of moderate intensity 200 min/week to a dietary weight loss program with or without advice to "sit less" in individuals with obesity (aged 65-85) involved in a 6-month supervised protocol. They found that the addition of the structured exercise intervention did not produce more weight loss than the combined weight loss and sit less program, nor the combination of weight loss, sit less and structured exercise. This finding emphasizes the importance of sitting less before moving more. In a systematic review and meta-analysis including data from 33 studies conducted in adults with normal weight or overweight (BMI 22.1 to 35.9 kg/m<sup>2</sup>), Hadgraft et al.<sup>104</sup> reported a small but significant effect of interventions aiming to reduce SB (2 weeks to <6 months) on body weight (-0.56 kg), waist circumference (-0.72cm) and percent body fat (-0.26%). Another meta-analysis including 18 studies of adults with metabolic disorders such as overweight/obesity or type II diabetes, cardiovascular and musculoskeletal diseases<sup>105</sup> reported that a reduction of 64 min/day in sedentary time was associated with decreased body fat (-0.66%) and waist circumference (-1.52 cm). In another systematic review and meta-analysis of 9 studies in adults with both normal weight and overweight (aged 45.3), Saeidifard et al.<sup>107</sup> concluded that replacing sedentary time with standing (+1.33 hours/day) was associated with reductions on body fat mass (-0.75 kg). These studies show that reducing sedentary time can promote weight loss. While these effects appear to be minor to moderate at an individual level, they could be beneficial at the population level and therefore be relevant from a public health perspective.

### *2.3.3. Effect of changes in physical activity and sedentary behaviors on weight loss maintenance*

Although data from the NWCR have identified regular PA, especially of moderate-to-vigorous intensity, as an important tool for long-term weight loss maintenance, RCTs have provided more conflicting

results. Several RCTs that examined the effects of increases in PA on weight loss maintenance in adults did not show protective effects of MVPA against weight regain following weight loss<sup>108-117</sup>. By contrast, Fanning et al.<sup>106</sup> found that body and fat mass regains 18 months after the cessation of a 6-month PA intervention were significantly lower in an intervention combining dietary restriction, an exercise program and advice to sit less when compared to the dietary restriction and structured exercise only arm. These differences were linked with greater total active time in the daylong movement intervention due to greater time spent in LPA, confirming the importance of moving throughout the day for weight management. More RCTs with interventions targeting both PA and SB and a tight monitoring of daily activities are needed to better understand the role of PA in weight loss maintenance.

In summary, promoting LPA, instead of or in addition to MVPA, and reducing SB appears to be promising strategies to increase the total volume of PA and induce body weight loss and maintain it over the long-term. This seems to be particularly true in sedentary-inactive adults (**Box 2**). This is however a new area of research and further studies are needed to better understand the populations that would benefit the most from interventions like this, how sustainable those changes are and what is the impact on activity EE and TDEE and consequently on body weight and adiposity. As is true for studies on exercise (or MVPA) training, the question of the dose-effect relationship will need to be addressed as well as whether increases in LPA, like increases in MVPA, can elicit compensatory responses that moderate expected effects. Understanding the interactions between the different components of energy balance and the factors regulating those interactions remains complex.

### **3. Energy balance regulation and body weight**

Regardless of the individual predisposition to develop obesity, only a chronic positive energy balance can lead to weight gain. If the concept of energy balance appears to be trivial, it conceals the complexity of the pathophysiology of obesity. Maintaining energy balance is dynamic process, not a steady state. It

is therefore important to investigate the effects of perturbations of one side of the energy balance equation on the other components to understand the behavioral and physiological compensations at play (**Box 3**). These compensations, volitional or not, have been thoroughly reviewed by King et al.<sup>118</sup>. Our intent is not to repeat their work but rather interpret these compensations in the context of changes in SB/LPA vs MVPA and attempt to draw some conclusions on the existence of potential thresholds above which compensations are triggered or not.

### 3.1. Effect of changes in physical and sedentary activities on energy expenditure

#### 3.1.1. *In adults with normal weight or overweight*

Total daily EE is defined as the sum of resting metabolic rate, diet-induced thermogenesis and activity-related EE (exercise and volitional activities). Theoretically, an increase in PA should lead to an increase in TDEE. Yet, spontaneous compensatory behavioral and physiological mechanisms seem to be recruited when PA increases<sup>118</sup>. Rowland<sup>8</sup> and Pontzer et al.<sup>9</sup> have argued that an increase in exercise-induced EE is compensated, at least above a certain level, by a decrease in non-exercise-induced EE, thus leading to a plateau in TDEE. When pooling data from the 2,500 adults from the Modeling the Epidemiological Transition Study (METS) cohort<sup>119</sup>, the authors assessed the relationship between TDEE measured with DLW adjusted for sex and anthropometric parameters and PA measured by accelerometry. Analyses showed a change point (*i.e.*, the activity level at which the slope of the change-point regression becomes indistinguishable from zero) around 230 counts per minute per day (CPM/day), which was estimated by the authors to an approximate TDEE of 2,600 kcal/day<sup>119</sup>.

To better understand the impact of increases in PA on TDEE in non-elite athletes, **table 1** summarizes a non-exhaustive list of studies during which free-living TDEE was assessed with the DLW method before and after an exercise protocol intervention. Overall, results reveal a great deal of heterogeneity. While some studies observed an increase in total EE after an exercise intervention<sup>90</sup>, others did not<sup>120-122</sup>. For example, the MET 2 study conducted in adults with overweight or obesity reported increases of

310 kcal/day in TDEE in responders (body weight loss >5% from baseline) after 10 months of supervised exercise 5 days/week with a controlled EE of 400 kcal or 600 kcal per exercise session (2,000 or 3,000 kcal/week)<sup>90</sup>. In a 2-month intervention consisting of moderate intensity aerobic exercise conducted in sedentary men with overweight or obesity, Lefai et al.<sup>100</sup> observed no change in total or activity-related EE due to a spontaneous decrease in non-training activity-related EE, associated with reduced time spent in LPA. This lack of change is consistent with the constrained TDEE theory<sup>9</sup> as their TDEE may have been close to a threshold value (3,368 kcal/day at baseline). However, in the same study the authors observed a significant increase in both activity and TDEE in sedentary male with normal weight adults after the same 2-month intervention on PA<sup>100</sup>, with an increase from 2,556 kcal/day at baseline to 2,938 after the intervention. Whybrow et al.<sup>123</sup> observed that young healthy individuals performing 40 min sessions on stationary bicycle targeting 3.3 kcal/kg of body weight for 16 days increased their TDEE to 3,272 kcal/day through exercise-induced EE. However, no change in body or fat mass was observed. In this study, subjects compensated for about 30% of the exercise-induced energy deficit by increasing EI. Nevertheless, a high degree of variability in compensation among individuals was reported by the authors. Indeed, several factors may influence the degree of energy compensation.

Recently, the International Atomic Energy Agency (IAEA) DLW database group combined data of DLW-derived TDEE in 1,754 adults and showed that adiposity has a strong association with the degree of compensation associated with PA through decreases in other components of TDEE<sup>124</sup>. People in the 10<sup>th</sup> percentile of BMI distribution compensate 27.7% of activity calories vs 49.2% for people in the 90<sup>th</sup> percentile. In other words, only 72.3% and 50.8% of additional activity-related EE actually translate into extra energy consumed during the day for the 10<sup>th</sup> and 90<sup>th</sup> percentile of BMI, respectively. That means that individuals with higher fat levels compensate more for energy expended in PA than those with lower adiposity. This goes along with the findings of the longitudinal PA intervention study conducted by Lefai et al.<sup>100</sup> and reported above. The recent study by Willis et al.<sup>125</sup> examined the relationship between PA and TDEE objectively measured in 584 older adults (aged 50-74) over a 6-month period. Their findings suggest that energy balance status, estimated based on the 6-month changes

in body mass, plays an important role in the degree of compensation for energy expended in PA. They showed that TDEE (adjusted on sex, ethnical and anthropometric parameters) increased with deciles of objectively-measured PA by 705 and 430 kcal/day between the bottom and top deciles for individuals in stable and positive energy balance (*i.e.*, with stable or higher body mass over 6 months compared to baseline, respectively). No difference was observed in individuals in negative energy balance (*i.e.*, lower body mass over 6 months compared to baseline) given that only a slight decrease of 56 kcal/day was observed between people at the bottom and the top deciles of PA. Goran et al.<sup>122</sup> however observed that elderly people (aged 56-78) maintained stable TDEE after an 8-week endurance training intervention at 60-85%  $\text{VO}_2\text{max}$  (from 2,408 kcal/day at baseline to 2,474 kcal/day after 8 weeks of intervention). No change in body mass or fat mass was observed. The terms (volume, intensity, frequency and duration) of PA training also seem to influence the impact of PA on TDEE and body weight. Riou et al.<sup>99</sup> compared the effect of 3 months low vs moderate intensity exercise training on EI, TDEE, time spent in LPA and SB and body weight. The two trainings were matched to induce similar extra EE of 1500 kcal/week. None of the PA intervention impacted EI and TDEE; a non-significant decrease in TDEE was observed in the moderate-intensity exercise training group (-173 kcal/day). However, participants in the moderate-intensity training group elicited greater reduction in daily walking time and higher increase in time spent lying down than participants in the low-intensity training group. These spontaneous behavioral adaptations indicate more pronounced energy compensation following moderate-intensity training compared to a low intensity exercise training protocol (161 vs 49% of the exercise-induced EE). These behavioral and energetic differences translated into about 1kg weight gain in the moderate-intensity training group vs 1kg weight loss in the low-intensity training group. Flack et al.<sup>126</sup> recently compared the metabolic effect of a 12-week aerobic training intervention consisting of 6 sessions per week of 40-60 min at 50-59 % heart rate reserve exercise to a calorie and intensity-matched training program consisting of 2 sessions per week of 90-120 min exercising in adults with overweight or obesity. Those in the 6 sessions per week group lost 1.04 kg of body weight and 1.82 kg of fat mass, while those in the 2 sessions per week group maintained stable body and fat mass. Interestingly, individuals in the 6 days/week group expended 85 kcal/day more than their counterparts. The total daily amount of exercise-

induced EE may be one of the factors triggering spontaneous behavioral and/or physiological compensations. Nevertheless, interindividual variability is important. For example, Herrmann et al.<sup>90</sup> observed responders and non-responders in both groups following a 6-month PA intervention targeting either 400 or 600 kcal/day in the MET2 study, with responders losing 8.4% of initial body weight and the non-responders maintaining initial body weight (-0.04%).

**- Please insert table 1 near here -**

Altogether these studies suggest that 1) increases in PA can raise TDEE above the hypothesized plateau of 2,600 kcal/day proposed by some research groups, at least in response to short/medium term interventions, 2) the modalities of PA training likely influence the propensity to compensate for exercise training EE, and 3) the impact of increases in PA on TDEE may depend on individual characteristics, *i.e.*, adiposity, habitual EE, age, energy balance status, and other factors. An important point that remains unknown is whether the behavioral and physiological compensatory mechanisms develop as people put on weight or whether compensations are a “pre-existing” condition as described in the “thrifty gene” theory<sup>127</sup>. In other words, do people accumulate fat mass because they compensate more, or do they compensate more because they have greater adiposity?

### *3.1.2. In adults with reduced weight*

If the role of PA in weight loss is highly debated, its role in preventing unhealthy weight gain and regain after weight loss is now generally accepted. More recent studies have furthered our understanding of the specific role of PA/SB in weight loss maintenance. In a cross-sectional study, Ostendorf et al.<sup>128,129</sup> observed that people who successfully maintained weight loss (maintaining  $\geq 13.6$  kg weight loss for  $\geq 1$  year) over the long-term expended more energy than people with normal weight with matched BMI or people with obesity whose BMI was similar to the BMI of the weight loss maintainers prior to weight loss. This greater TDEE was associated with higher activity-related EE and PAL values (1.75 vs 1.61 vs



1.55 for the successful weight loss maintainers, individuals with normal weight, and those with obesity, respectively). Furthermore, the weight loss maintainers, like the individuals with normal weight, spent more time in LPA and less in SB than people with obesity, but also spent more time in MVPA than both other groups. This study suggests that maintaining weight loss over the long term is associated with high levels of both LPA and MVPA and reduced sedentary time. It further supports previous findings indicating that a minimum PAL of 1.7-1.8 is required to prevent excessive weight regain.

In 2003, experts at a consensus meeting were already suggesting that moderate intensity activity of approximately 45-60 minutes per day, or 1.7 PAL, was likely sufficient to prevent the transition to overweight or obesity, and 60-90 minutes of moderate intensity activity, or 1.8 PAL, were required to prevent weight regain in individuals with former obesity<sup>14</sup>. Regardless the exact PAL value, it is substantially below the maximal sustainable PAL of 3.5 described by Thurber et al.<sup>12</sup>. The same is true for the PAL of the general population (i.e., 1.7-1.8)<sup>13</sup>, which is much lower than the hypothetical maximal values. Therefore, the constrained energy model does not exclude a major role of PA in body weight regulation, and future longitudinal studies are needed to clarify the relationships between PA/SB and TDEE. However, focusing our attention on TDEE only, without considering the direct and indirect effects on EI would be misleading. It is only by integrating the effects of PA/SB on both sides of the energy balance equation that we will be able to fully understand their respective effects on the regulation of body mass and composition.

### 3.2. Effect of changes in physical and sedentary activities on energy intake

The study of the relationship between PA and food intake is not new. In the 1950s following observations in Bengali workers, the French-American nutritionist Jean Mayer described that EI was closely coupled with EE at medium to high levels of PA in a “regulated zone”. However, at low levels of PA, the coordinated regulation of appetite and energy balance was altered so that EI exceeded

requirements and led to weight gain<sup>130</sup>. EI being mediated by appetite signals, various studies suggest a “J-shaped curve” between the whole spectrum of PA (*i.e.*, from very low to very high level) and appetite regulation<sup>57,130,131</sup>. Hedonic and behavioral systems regulating EI may be altered in environments where food is consumed in excess. These dysregulations may overpower biologic systems<sup>132</sup> and amplify the disequilibrium of energy balance.

The concept of “energy flux”, defined as “the magnitude of total energy turnover while maintaining energy balance over periods of weeks to months”<sup>11</sup>, can help us better understanding these different observations. This concept suggests that increasing PA would allow higher EI to balance higher EE in a state of high energy flux. When compared with a state of low energy flux, high energy flux may better regulate weight and fat gain and limit weight regain<sup>10,11</sup>. This approach might be more sustainable than decreasing EI to match low PA over prolonged periods of time. However, the way energy is expended should be considered, rather than just TDEE<sup>11</sup>. Shook et al.<sup>133</sup> conducted a 1-year follow up in 421 male adults with normal weight. The authors observed higher weight gain in the least active people compared to their most active counterparts. This was partly explained by an incapacity to reduce EI during the period of reduced PA, potentially due to a failure to generate or respond to satiety signals<sup>134</sup>. While SB should be taken into account in the complex relationship between PA pattern and energy balance, its characterization (*i.e.*, type of SB) should be specifically considered<sup>135</sup>. Cross-sectional population studies have shown associations between time spent in TV viewing or screening and unhealthy diet habits (*i.e.*, higher consumption of energy-dense snacks and sugar-sweetened beverages, less fruit and vegetables consumption) in children and adolescents<sup>136,137</sup>. In an interventional study, Chaput et al.<sup>138</sup> observed that adolescents (average age 16.7 y.o.) spending 1-hour playing video games increased their EE and EI compared with a resting alone condition, resulting in a 163 kcal-positive energy balance. The same research group observed that EE was similar after a “knowledge-based work” task or a control resting condition in 15 healthy adults women (average age 24.1 y.o.), while *ad-libitum* EI increased leading to positive energy balance in the intervention group<sup>138</sup>. Cognitively demanding tasks have been shown to have different physiological consequences and energy sources than physically demanding

tasks. This might be explained by a higher glucose demand from the brain and the need to restore glucose homeostasis, or an increased stress-induced cortisol secretion<sup>135</sup>. Considering the context in which physical and sedentary activities are performed remains an understudied area and further research is needed. This is particularly important to better understand the overall impact of the technological and digital revolutions that have drastically modified our work and lifestyles.

In contrast to SB, high levels of PA improve homeostatic control of appetite in response to acute disturbances<sup>139</sup>. Stubbs et al.<sup>134</sup> observed that being moderately active provided better regulation of food intake than being sedentary following *ad libitum* meal, despite no change in hunger, appetite or weight. Myers et al.<sup>140</sup> reported negative associations between disinhibition and binge eating and both LPA and MVPA (assessed during one week in free-living conditions with accelerometers) in people with overweight or obesity. They further observed that the most inactive individuals had higher fat mass, and that fat mass was strongly correlated with appetite disorders suggesting a bidirectional relationship between physical inactivity and obesity. Habitual activity seems to further influence the effect of increases in PA. The E-MECHANIC trial that prescribed structured PA of 8 or 20 kcal/kg of body weight per session during a 24-week intervention in adults with overweight or obesity showed that habitual baseline MVPA levels, not the activity-related EE, predict changes in EI and body weight<sup>91</sup>. In a recent cross-over randomized study<sup>141</sup>, we showed in lean healthy people that prolonged sitting (>30 minutes) was associated with greater food cravings before a meal compared to a day during which sedentary activities were frequently interrupted by short bouts of moderate intensity PA, thus indirectly supporting the adverse effect of SB on food intake control.

These studies provide new perspectives about the roles of PA and SB in the regulation of body weight through alterations in appetite regulation. They suggest that while PA likely improves appetite control to match food intake with changing energy requirements, SB likely compromises this homeostatic regulation thus promoting positive energy balance. Importantly this coupling between PA, appetite and EI may be primarily influenced by energy flux, but further investigations are needed to better understand the interaction between PA/SB, food intake control and the regulation of energy balance (**Box 3**).

- Please insert box 3 near here -

Some studies suggest that food intake may be determined by lean body mass<sup>142,143</sup>, especially under energy deficit conditions during which the restoration of fat-free mass may become a priority for the body. Others have shown that 24-hour EE is the major determinant of EI<sup>144,145</sup>. Despite heterogeneity in protocol modalities (*e.g.*, type of exercise, duration and intensity, chronicity, etc.), other data argue in favor of a beneficial effect of PA on the appetite through hormones secretion in order to reach the targeted “reference” weight<sup>146</sup>. For example, Martins et al.<sup>147</sup> observed an improvement in appetite control following 6 weeks of moderate exercise training in 29 healthy sedentary adults. King et al.<sup>148</sup> found that the increased fasting hunger following a 12-week exercise protocol in men and women with overweight and obesity was accompanied by increased satiation following a fixed meal, partially explained by an increase in anorexigenic hormones release, such as glucagon-like peptide 1 (GLP1). Flack et al.<sup>126</sup> reported in participants with overweight or obesity that greater reductions in postprandial leptin concentration following a 12-week exercise intervention were associated with lower energy compensation (difference between estimated and actual changes in body composition). The authors suggested that reductions in the levels of postprandial leptin indicate an improvement in leptin sensitivity with exercise training which helps controlling food intake. During a two-month bedrest study<sup>149</sup>, a model that induces extreme levels of physical inactivity and sedentariness, we observed that lean healthy active women were able to adjust their EI to the very low levels of PA, and that fasting leptin was negatively associated with spontaneous EI, thus also suggesting some relationships between PA, leptin and food intake. The mechanisms underlying the relationships between PA and food intake still warrant further investigations though.

### 3.3. The protective effects of physical activity against overfeeding

It has been suggested that overfeeding might trigger adaptive physiological responses to dissipate excess energy in order to achieve energy balance and maintain a stable weight by increasing TDEE. Levine et al.<sup>20</sup> observed that following 8 weeks of over-nutrition in adults with normal weight, those that spontaneously increased their PA the most gained the least amount of body fat. An early study by Ravussin et al.<sup>150</sup> found an increase in TDEE following 9 days of overfeeding of which one third was explained by increased basal metabolic rate. However, only 25% of the excess energy consumed was dissipated through an increased EE, the other portion being stored in the body. More recently, Johannsen et al.<sup>151</sup> conducted a longer overfeeding protocol (8 weeks) and found a significant increase in TDEE driven by an increase in sleeping metabolic rate. Even if this increase was statistically significantly, from a clinical point of view it was insufficient to prevent weight gain. Long-term overfeeding studies described an increase in body weight that was slowing down as the intervention was sustained over several months, likely due to increases in both resting metabolic rate and energy costs to move a heavier body<sup>152</sup>. None of these studies observed increasing levels of PA thought to be protective against weight gain like it was initially suggested in the study by Levine et al.<sup>20</sup> Finally, the existence and magnitude of these adaptations are still debated<sup>151</sup> in part due to the large inter-individual variability observed in these studies<sup>152</sup>. Results suggest that the dynamic processes that maintain stability of energy balance over time (*i.e.*, simultaneous increase or decrease in EE with increases or decreases in EI) are complex and need further investigation (**Figure 3**).

- Please insert figure 3 near here -

#### 4. Effect of physical activity and sedentariness on nutrient oxidative balance

In addition to a stable energy balance, a second condition is required for the maintenance of a stable body weight: stable oxidative balances. This means the amounts of substrates consumed by the body need to be oxidized. As elegantly explained by the two-compartment model of Jean-Pierre Flatt<sup>153</sup>, oxidative balance is influenced by the capacity to store each macronutrient in the body. Proteins

being required for the structure, function, and regulation of the body’s tissues and organs, their balance is tightly regulated by the organism. Because the storage of carbohydrates (CHO) is limited to few hundred grams essentially in skeletal muscles and the liver, changes in CHO intakes induce large variations in the level of the glycogen stores which are rapidly adjusted by their oxidation. Conversely, changes in fat intake cause only small variations in the level of the large stores of fat in the body and are not followed by equivalent changes in lipid oxidation. Fat balance has been shown to be tightly linked to energy balance and plays an important role in body mass and composition management<sup>154</sup>.

By lowering glycogen stores, exercise can promote fat oxidation<sup>154</sup>. By contrast, low levels of PA reduce the ability of the body to use lipids as substrates for meeting energy needs<sup>155</sup>, and promote the development of metabolic inflexibility (*i.e.*, incapacity for an organism to adjust fuel oxidation to changes in fuel availability<sup>156,157</sup>). The concept of metabolic flexibility implies that metabolic health is determined by the ability to adapt to conditions of temporary stress, such as overfeeding or exercise, and thus maintain or regain homeostasis. Previous studies have shown that activity-related EE, but not TDEE, predicts nutrient partitioning<sup>158</sup> and metabolic flexibility<sup>159-161</sup>. Importantly, these associations between activity-related EE, nutrient partitioning and metabolic flexibility were observed independent of detectable changes in energy balance, and even in the absence of an increase in TDEE<sup>100</sup>. Finally, it has been shown that the inability to both decrease time spent sedentary and adjust fuel use (metabolic inflexibility) to an acute overfeeding episode was correlated with long-term weight gain<sup>82,162</sup>. Altogether, these studies suggest key roles for PA, SB and activity-related EE in the regulation of oxidative balance and metabolic flexibility, two key factors involved in the regulation of body weight<sup>161</sup> (**Box 4**).

**Please insert box 4 near here -**

**Conclusion & future directions**

Despite decades of research, the epidemic of obesity is still growing worldwide likely because the causes of weight gain are still debated. The role of PA in body weight regulation has been greatly questioned

recently. However, a large body of data shows that high volumes of PA and limited sedentariness are associated with lower body weight, lower rates of weight gain, lower rates of obesity and less regain following weight loss. High levels of PA also contribute to improve body composition, metabolic parameters and appetite control, which are key determinants of energy balance, and hence body weight regulation. However, promoting MVPA is often associated with compensatory increases in sedentariness and EI and decreases in non-exercise EE that counteract the beneficial impact of MVPA on TDEE at least in people at-risk for or with overweight and obesity and/or with low habitual PA. These physiological and behavioral compensations reduce the beneficial effects of MVPA in the treatment of unhealthy weight gain. Recent data show that promoting LPA along with reducing SB are promising alternative/complementary strategies to increase total daily PA and EE that may not trigger spontaneous energy compensations to the same degree as MVPA. These findings support a role for PA/SB in body weight regulation, especially when viewed from a public health perspective. The recent research focus on MVPA in the treatment of obesity and the study of the effects of very high levels of PA on TDEE have provided useful insights into our understanding of the regulation of TDEE and the role that compensatory responses play in moderating the effects of a PA intervention. However, the dominance of these ideas may have overshadowed the important role that promoting PA could play in improving human health in our current environment. From a public health perspective, promoting PA, especially LPA, along with reducing/fragmenting SB may be important strategies to combat the obesity epidemic. Further studies are however needed to provide rigorous and robust data to support this message and develop practical strategies to increase PA and prevent SB at the population level.

In a broader perspective, a potential reason for our failure at combatting the obesity epidemic is that the complex interactions between biological, behavioral, and socio-ecological factors and their respective role in the regulation of body weight are still not well understood. Our view is that as long as PA is above a certain threshold level, diet, genes and other factors play a role, but their contribution is less pronounced. To address this complexity, future research will need to:

- Consider and objectively measure daily LPA and SB.

- Consider that the role of PA in the primary prevention of weight gain may differ from its role in the prevention of weight regain after weight loss. In the context of weight gain, PA is an environmental factor that contributes to induce a positive energy balance when low levels of PA are not matched by low levels of EI. Following weight loss, PA is now rather a tool to combat the biological mechanisms that are driving weight regain. The role of PA in these two distinct biological contexts require specific research; yet studies in people who have lost weight are still missing.
- Dissociate PA and PA-related EE. Although these two are closely related, PA refers to behaviors and body movements, and PA-related EE corresponds to the metabolic cost associated with PA. Measuring PA-related EE objectively requires combining the DLW method and indirect calorimetry. Raw data (*i.e.*, unadjusted) of PA-related EE should no longer be presented as it is prone to misinterpretation. While an adult with overweight can have PA-related EE as high as an adult with normal weight, the former results from the high cost of moving a large body while the latter is explained by high levels of daily PA. Data adjusted for body mass/composition should be presented in the future.
- Conduct adequately-powered RCTs to examine the influence of PA/SB on weight regulation. These studies should consider potential confounding variables such as habitual PA, maximal aerobic capacity, the type of PA and SB performed, the context in which the physical and sedentary behaviors are undertaken, food intake habits, sleep pattern, sex, etc.
- Consider interdisciplinary approaches that will aim to determine the relative contribution of the environmental, socio-ecological and biological factors in body weight regulation. As we recently discussed it in a viewpoint<sup>37</sup>, studying populations that have maintained a pre-industrial lifestyle and are facing rapid and drastic environmental changes due to modernization may help reaching this goal.



748 In conclusion, rigorous research is still needed to fully understand the role of physical activities (i.e.  
749 MVPA, LPA and SB) in the regulation of body weight, and to develop efficient and easy-to-  
750 implement strategies for improving obesity management.

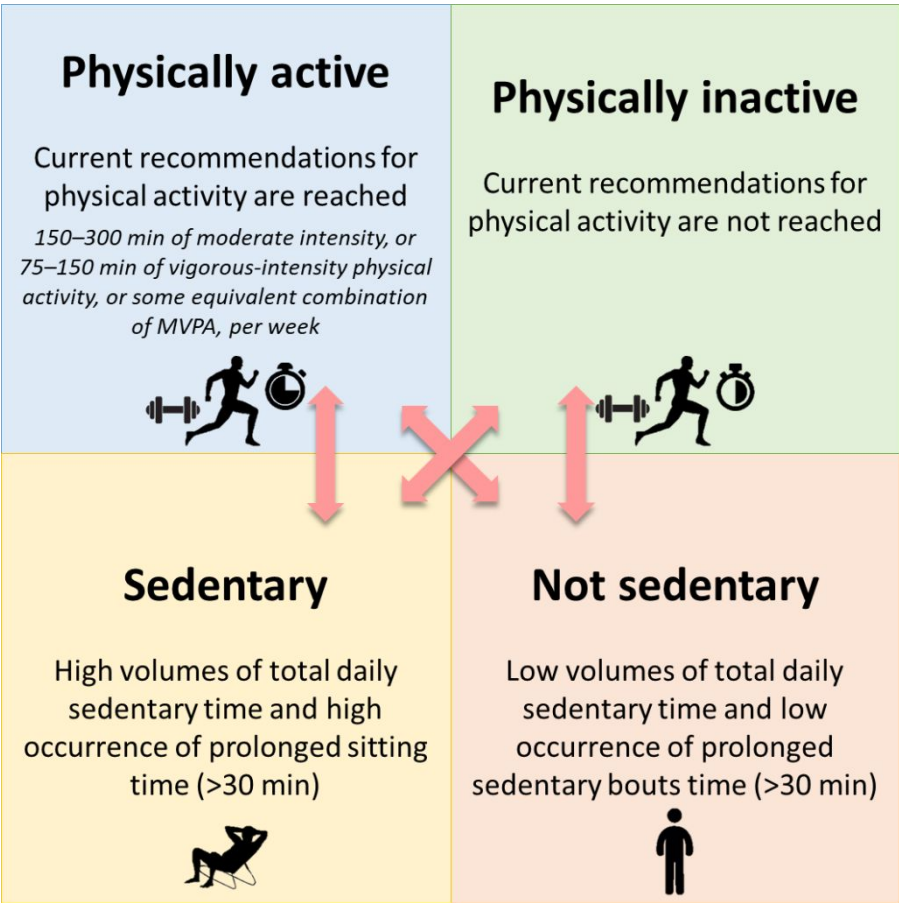
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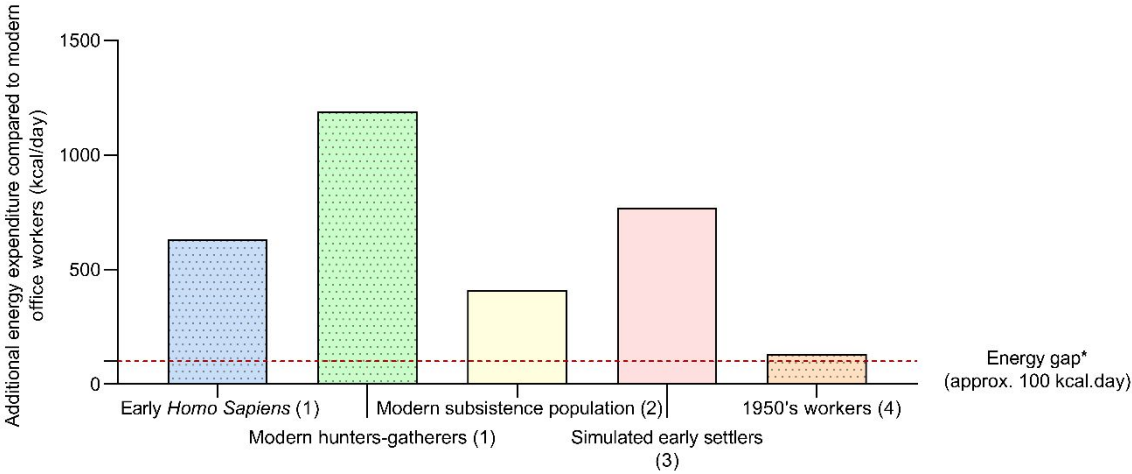
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Figures

Figure 1:



759    Figure 2

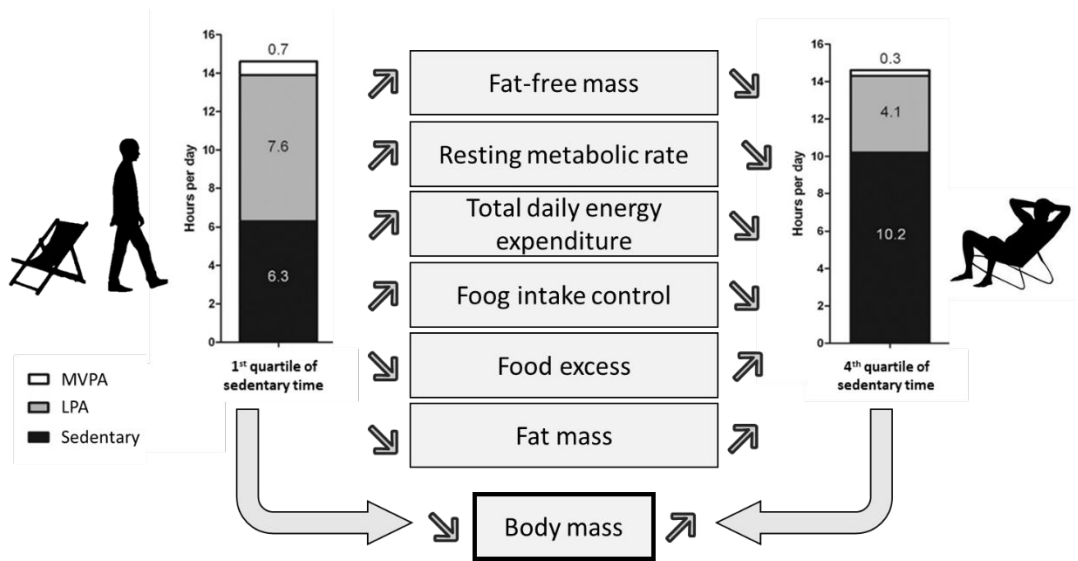


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763 Figure 3:



## Figures legend

Figure 1: Schematic representation of the four observable behaviors across the spectrum of physical activity and sedentary behavior. Of note, no specific recommendations currently exist for being or not being sedentary.

*Abbreviation: MVPA: moderate-to-vigorous physical activity*

Figure 2: Schematic representation of the extra energy expended by early *Homo sapiens*, modern hunter-gatherers, modern subsistence populations, and workers of the 1950's compared to the total daily energy expenditure of modern office workers. Spotted barres represent estimated data, and plain barres represent measured data.

*(1) estimated by Cordain et al. (1998)<sup>50</sup>; (2) measured by Leonard (2010)<sup>51</sup>; (3) measured by Egger et al. (2001)<sup>163</sup>; (4) estimated by Church et al. (2011)<sup>54</sup>; \* Hill (2013) estimated an energy gap (energy intakes – energy expenditure) of about 100 kcal per day that likely explains the obesity epidemic at the population level.*

Figure 3: Schematic representation of the effects of sedentary behaviors on the components of energy balance and hence, body weight regulation. Using the data of Owen et al.<sup>164</sup>, the left side of the figure represents a non-sedentary person (10<sup>th</sup> percentile of total daily sedentary time) while the right side of the figure represents a highly sedentary person (90<sup>th</sup> percentile of total daily sedentary time).

*Abbreviation: MVPA: moderate-to-vigorous physical activity; LPA: light physical activity*

789 **Table**

790  
791 **Table 1: Interventional studies that tested the effects of increases in physical activity on doubly-labelled water-derived total daily energy expenditure**  
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Author	Year	Population	Intervention	Changes in total daily energy expenditure	Changes in obesity markers	Differences between group
Goran et al. <sup>122</sup>	1992	6M (age: 68 (SD 7) y.o.; BMI: 24.9 (2.3) kg/m <sup>2</sup> )	8 weeks of endurance training at 60-85% VO2max	From 2,408 (SD 478) to 2,474 (497) kcal/day	BM: from 71.11 (SD 8.50) to 71.07 (8.41) kg	No significant ↓ BM  Significant ↓FM
		5W (age: 63 (5) y.o.; BMI: 24.0 (3.2) kg/m <sup>2</sup> )	No control group		FM: from 21.58 (6.64) to 20.68 (6.61) kg	
Herrmann et al. <sup>90</sup>	2015	31 M / 31 W (age: 22.6 (SD 4.2) y.o.; BMI: 31.2 (4.8) kg/m <sup>2</sup> )	6 months of aerobic training targeting 400 or 600 kcal/week	<i>Responders</i> <sup>a</sup> : from 2,866 (SD 598) to 3,137 (658) kcal/d	<i>Responders</i> <sup>a</sup> : BM: −8.4 (SD 3.8) %	↓BM: <i>Responders</i> > <i>Non-responders</i> despite no different changes in energetic outcomes
		Creation of groups <i>a posteriori</i> based on percent weight loss at 10 months <sup>a, b</sup>		<i>Non-responders</i> <sup>b</sup> : from 3,000±737 to 3,169±675 kcal/day	<i>Non-responders</i> <sup>b</sup> : BM: −0.04 (2.5) %	
Hunter et al. <sup>120</sup>	2015	n=140W randomly assigned in one of the three groups  <i>Aerobic</i> (age: 35.2 (SD 7.0) y.o.; BMI: 28.5 (1.5) kg/m <sup>2</sup> )	<i>Aerobic</i> : 3-5 times/week during 8 weeks treadmill walking / jogging (20 to 40 min at 67 to 80% HR <sub>max</sub> )	<i>Aerobic</i> : from 2,095 (SD 392) to 2,032 (329) kcal/d	<i>Aerobic</i> : BM: from 76.9 (SD 6.7) to 64.4 (6.1) kg FM: from 33.9 (5.0) to 22.0 (4.6) kg (from 44.0 (3.7) to 33.3 (4.6) %)	↓BM and ↓FM: No difference between the groups

		<i>Resistance</i> (age: 33.9 (6.1) y.o.; BMI: 28.1 (1.2) kg/m <sup>2</sup> )	<i>Resistance</i> : 3-5 times/week during 8 weeks with 1 to 2 sets of 10 rep. at 65% to 80% 1 RM with 2 min rest between sets.	<i>Resistance</i> : from 1,905 (346) to 1,968 (290) kcal/d	<i>Resistance</i> : BM: from 77.5 (7.6) to 65.9 (6.5) kg FM: from 33.7 (5.2) to 21.7 (4.3) kg (from 43.0 (3.6) to 32.4 (4.5) %)	↓%FM: <i>Resistance</i> > <i>Aerobic and No exercise</i>
		<i>No exercise</i> (age: 35.6 (5.5) y.o.; BMI: 28.2 (1.4) kg/m <sup>2</sup> )	All subjects were provided an 800-kcal diet until reach a BMI <25 kg/m <sup>2</sup>	<i>No exercise</i> : from 2,194 (271) to 1,953 (388) kcal/d	<i>No exercise</i> : BM: from 78.1 (6.9) to 65.9 (-6.3) kg FM: from 33.4 (4.8) kg to 22.4 (4.5) kg (from 42.7 (3.4) to 33.5 (4.7) %)	
Wang et al. <sup>165</sup>	2017	<i>Lower dose</i> : 37 W (age: 65.7 (SD 4.5) y.o.; BMI: 25.5 (3.9) kg/m <sup>2</sup> )  <i>Higher dose</i> : 35 W (age 65.2 (4.1) y.o.; BMI: 25.8 (3.0) kg/m <sup>2</sup> )	Walking protocol at 50-55% HR <sub>reserve</sub> to achieve 8.0 or 14.0 kJ/kg body weight weekly, respectively	<i>Lower dose</i> : from 2,093 (SD 226) to 2,109 (293) kcal/d  <i>Higher dose</i> : from 2,056 (307) to 2,126 (383) kcal/d	BM: -0.8 (SD 2.1) kg FM: -0.9 (1.8) kg  <i>Results are provided as an average for both groups</i>	No significant ↓BM and ↓FM in both groups

Abbreviations: BM: body mass; FM= fat mass; M= men; SD= standard deviation; W= women

<sup>a</sup>: responders lost ≥5% of baseline body weight in response to a 10-month supervised exercise training program with verified levels of exercise-induced energy expenditure

<sup>b</sup>: responders lost <5% of baseline body weight in response to a 10-month supervised exercise training program with verified levels of exercise-induced energy expenditure

794 **Box**

**Box 1: The physical activity transition**

- Drastic and rapid changes in PA/SB occurred in every domain of daily life (work, leisure, daily life, etc.) over the past century.
- Only 20% of the global population currently reaches PA guidelines when objectively assessed.
- In high income countries, people spend more than 8 hours/day in SB.
- Likely due to these changes in PA/SB, the TDEE of modern humans living in high income countries is estimated to be lower than that of our ancestors, the early *Homo Sapiens*.
- The PA transition has created a mismatch between our evolutionary human history and the modern built and social environments which contributes to the emergence of the “diseases of civilization”.
- The role of the PA transition in the epidemic obesity is however still a topic of debate.

**Box 2: Effects of changes in PA and SB on obesity biomarkers**

- The modest effect of exercise training (i.e. MVPA) on weight loss (1-2kg lost on average) has been used to argue that PA does not play a role in body weight regulation.
- However, the role of PA in weight loss maintenance is well accepted.
- Prolonged bouts of SB (>30 min) are positively associated with unhealthy weight gain.
- Increasing LPA instead of MVPA may be an easier strategy to implement in daily life for sedentary inactive people with overweight or obesity.
- Cross-sectional and longitudinal studies report beneficial associations between greater PA and lower SB and measures of obesity and weight gain.
- Well-powered randomized controlled trials are needed to better understand the respective effect of MVPA, LPA and SB on body weight regulation.



**Box 3: Effects of changes in PA and SB on the components of energy balance**

- High energy flux via high levels of PA allows better coupling between EE and EI than low energy flux.
- Control of appetite and EI is dysregulated in inactive and sedentary individuals compared to physically active people.
- Increases in PA, especially MVPA, can trigger spontaneous behavioral and/or physiological compensatory responses that diminish the impact of PA-related EE on TDEE and/or induce increases in EI.
- A large inter-individual variability exists in the effects of PA on TDEE and body weight.
- Changes in TDEE in response to increases in PA are influenced by body weight status, adiposity, energy balance status, age and exercise modality.
- Increasing LPA and decreasing SB, instead of increasing MVPA, may elicit less energy compensation, and therefore lead to greater increases on TDEE and energy deficit.

**Box 4: Effects of changes in PA and SB on nutrient metabolism and metabolic flexibility**

- Low levels of PA reduce the ability of the body to use lipids as substrates for meeting energy needs.
- High levels of daily PA and SB are respectively positively and negatively associated with the ability of the body to adjust substrate use to changes in nutrient availability (i.e. metabolic flexibility).

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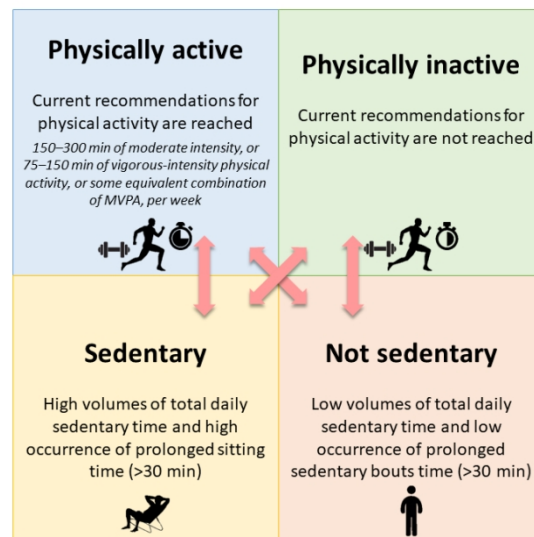


Figure 1: Schematic representation of the four observable behaviors across the spectrum of physical activity and sedentary behavior. Of note, no specific recommendations currently exist for being or not being sedentary. Abbreviation: MVPA: moderate-to-vigorous physical activity

338x190mm (96 x 96 DPI)

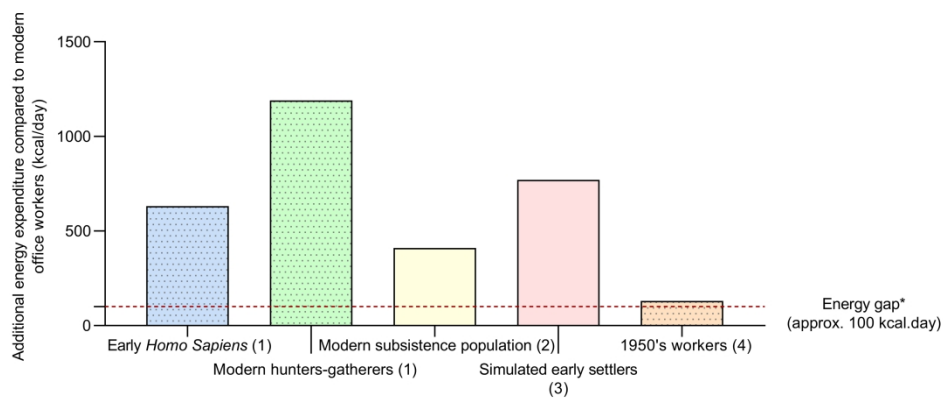


Figure 2: Schematic representation of the extra energy expended by early *Homo sapiens*, modern hunter-gatherers, modern subsistence populations, and workers of the 1950's compared to the total daily energy expenditure of modern office workers. Spotted barres represent estimated data, and plain barres represent measured data. (1) estimated by Cordain et al. (1998)50; (2) measured by Leonard (2010)51; (3) measured by Egger et al. (2001)163; (4) estimated by Church et al. (2011)54; \* Hill (2013) estimated an energy gap (energy intakes – energy expenditure) of about 100 kcal per day that likely explains the obesity epidemic at the population level.

179x76mm (600 x 600 DPI)

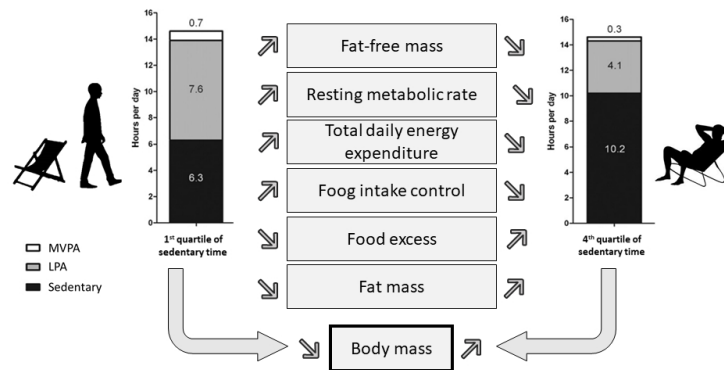


Figure 3: Schematic representation of the effects of sedentary behaviors on the components of energy balance and hence, body weight regulation. Using the data of Owen et al.<sup>164</sup>, the left side of the figure represents a non-sedentary person (10th percentile of total daily sedentary time) while the right side of the figure represents a highly sedentary person (90th percentile of total daily sedentary time). Abbreviation: MVPA: moderate-to-vigorous physical activity; LPA: light physical activity

338x190mm (96 x 96 DPI)