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► To cite this version:

Pierre Bourdier, Chantal Simon, Daniel Bessesen, Stéphane Blanc, Audrey Bergouignan. The role of physical activity in the regulation of body weight: The overlooked contribution of light physical activity and sedentary behaviors. *Obesity Reviews*, 2023, 24 (2), pp.e13528. 10.1111/obr.13528 . hal-03856989

HAL Id: hal-03856989

<https://hal.science/hal-03856989v1>

Submitted on 25 Nov 2022

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1 **Title:**

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

4

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14

15 **Keywords:** physical inactivity, sedentary behaviors, energy balance, weight management

16

17 **Running title:** Physical activity, sedentary behaviors & body weight regulation

18

19 **Acknowledgments:** This publication was made possible by funding to PB from the Graduate School
20 Life Science ED 414 of the University of Strasbourg, by funding to DHB from the Colorado National
21 Obesity Research Center (NORC, P30DK048520), by funding to AB from the NIH/NIDDK
22 (R01DK12334) and the NORC (NORC P30DK048520).

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33 **Conflicts of interest**

34 The authors have no conflicts of interest to declare.

35

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

49

50 **Abstract**

51 (192 /200 words)

52 The role of physical activity (PA) in the regulation of body weight is still a major topic of debate. This
53 may be because studies have essentially focused on the effects of moderate/vigorous PA (or MVPA) on
54 body weight while overlooking the other components of PA, namely light-intensity PA (LPA, daily life
55 activities) and sedentary behaviors (SB, too much sitting). In this review, we will (i) describe the history
56 of changes in PA behaviors that occurred with modernization, (ii) review data from cross-sectional and
57 longitudinal studies that examined the associations between PA, SB and measures of obesity, (iii) review
58 interventional studies that investigated the effects of changes in PA and SB on body weight and
59 adiposity, and (iv) discuss experimental studies that addressed potential biological mechanisms
60 underlying the effects of PA and SB on weight regulation. Overall recent findings support the
61 importance of considering all components of PA to better understand the regulation of energy balance
62 and suggest an important role for LPA and SB in addition to MVPA on body weight regulation.
63 Longitudinal large-scale rigorous studies are needed to advance our knowledge of the role of PA/SB in
64 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 controversial¹⁻⁷. 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 1998⁸ in which total daily EE (TDEE) is
76 homeostatically regulated, *i.e.*, controlled around a fixed value. Pontzer et al.⁹ 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)¹⁰. 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 accepted¹¹.

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 competitors¹², not in the general
89 population whose PAL values are between 1.4-1.8^{13,14}. Maintaining PAL values around 1.7-1.8 has been
90 estimated to be enough to prevent body weight gain and regain after weight loss¹⁴⁻¹⁶. These observations
91 support a role for PA in body weight regulation in the range of PALs observed in the general population.

92 In addition, research has tended to overlook the contribution of non-exercise activities (mainly
93 composed of light intensity physical activities – LPA, *i.e.*, PA associated with metabolic equivalents –
94 METs comprised between 1.6 and 2.9¹⁷), which correspond to activities of everyday life and any body
95 movement, such as walking, taking the stairs, gardening^{18,19} or activities other than volitional structured
96 exercise^{20,21}. These non-exercise activities are known to account for a large component of EE even in
97 sedentary individuals. In addition, time spent in LPA is negatively, but tightly, associated with time
98 spent in sedentary behaviors (SB)²². As trivial as it sounds, the more a person moves, the less time he/she
99 spends in sedentary activities.

100 Research on SB has gained increasing attention over the past 10 years, especially with the development
101 of activity monitors that allow to specifically measure this behavior. While the terms physical inactivity
102 and SB are used interchangeably^{23,24}, they are fundamentally different. Physical inactivity is defined as
103 engaging in less PA than necessary to meet current public health guidelines, *i.e.*, 150-300 min of
104 moderate to vigorous or 75-150 min of vigorous PA or an equivalent combination of moderate-to-
105 vigorous PA (MVPA, PA characterized by an EE > 3 METs)^{17,25}. By contrast, SB are defined as “any
106 waking behavior characterized by an EE ≤ 1.5 METs, while in a sitting, reclining or lying posture” based
107 on the terminology consensus of the Sedentary Behaviors Research Network (SBRN)²⁶. Based on these
108 definitions, an individual can paradoxically be both physically active and sedentary (**Figure 1**). Despite
109 the wide promotion of PA recommendations, most people engage in high amounts of sedentary
110 activities, *i.e.*, more than 55% of awake time²⁷. In a meta-analysis regrouping 1 million men and women,
111 Ekelund et al.²⁸ estimated that high levels of PA seem to be necessary to eliminate the increased risk of
112 death induced by more than 8 hours per day spent in SB, a duration commonly observed in office
113 workers²⁹. Despite the associations between SB and chronic diseases³⁰, there is a surprising lack of
114 information on the roles that SB and physical inactivity play in the increasing prevalence of obesity.

115 **- Please insert figure 1 near here -**

116

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

126

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

128 1.1. Physical activity patterns from ancient times to the present

129 Current human physiology and behavior are the result of natural selection in *Homo Sapiens* who
130 emerged about 200,000 years ago. In the Paleolithic era (approx. 40-50,000 years ago), our ancestors
131 hunted and gathered food. These activities required sustained activities at high levels of EE for 1-2
132 hours/day. Moreover, inactive periods were probably composed of squatting, kneeling or otherwise
133 sitting in postures that required continuous very low to low intensity muscle activity limiting the
134 deleterious effects of sedentariness that are observed in current industrialized populations³¹. With the
135 development of agriculture (approx. 10,000 years ago), humans needed to perform moderate intensity
136 activities for 6-8 hours/day³². The former “intermittently active” lifestyle corresponding to cycles of
137 short bouts of intense activities alternating with long resting periods was replaced by continuous and
138 sustained bouts of moderate intensity activity that were necessary to perform agricultural tasks without
139 the benefit of modern technology. Lightfoot³² estimated that non-technological agricultural activity
140 required 3-5 fold more active time than hunting/gathering. Although activity-related EE was similar

141 between both pre-industrial populations, it was significantly higher than what has been measured in
142 modern westernized populations³².

143 While PA pattern progressively changed over several millennia, rapid and major changes have occurred
144 over the past 200 years. Since the Industrial Revolution (end of the 19th century in the United Kingdom),
145 and more recently with the Great Acceleration (second half of the 20th century), industrial, technological
146 and digital advances have resulted in societal and behavioral changes in PA habits³³. The former
147 "traditional" environment, characterized by relatively scarce food and high EE, gave way to the modern
148 "social" and "built" environment that promotes obesogenic behaviors. Today, being physically inactive
149 does not jeopardize access to food due to the abundance of low-cost, high-fat, energy-dense food³².
150 These changes in habitual PA pattern are however not uniform worldwide³⁴. The prevalence of physical
151 inactivity is negatively associated with the Human Development Index (HDI, a statistic composite index
152 of life expectancy, education, and per capita income, used to rank countries into four tiers of human
153 development)^{35,36}. Populations living in countries associated with the lowest HDI quartile have a
154 significantly lower prevalence of physical inactivity than those in the highest quartile. Populations that
155 have completed the epidemiological transition (*i.e.*, shift in the causes of death from deaths due to high
156 children mortality and infectious diseases to deaths due to lifestyle-related and chronic diseases) along
157 with their nutritional and physical activity transitions are particularly vulnerable to physically inactive
158 and sedentary lifestyles³⁷.

159

160 1.2. Modern life: Widespread adoption of sedentary and physically inactive lifestyles

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

166 between 2011 and 2016, and keeps increasing⁴⁰. These data based on self-reported population-based
167 surveys likely overestimate PA⁴¹. For example, while 51% of the U.S. population self-reported reaching
168 recommended levels of PA in the National Health and Nutrition Examination Survey (NHANES study,
169 2003-2004), only 5% of individuals actually achieved these levels when data were objectively collected
170 with an accelerometer⁴².

171 Along with this reduction in PA, time spent in sedentary activities has increased in every sphere of daily
172 life. For example, time spent watching TV has increased by 61.4% in U.S. adults between 1950 and
173 2000 reaching up to 8 hours per day⁴³. By contrast, the time children and adolescents spend watching
174 TV decreased by approximately 23% between 1981 and 1997. This was associated with a concomitant
175 decrease in free-time by 12% mostly explained by an increased time away from home, primarily in
176 school, day care, and after-school programs⁴⁴. Nowadays, 86% of workers have sedentary jobs, spending
177 66% of their total work time sitting⁴⁵, with a reciprocal reduction in physically active tasks. The
178 expansion of the service sector of the economy has reduced time spent physically active in the workplace
179 by 32% since 1960. A further drop of 45% is expected by 2030 in the U.S. and a reduction from 19% to
180 35% in the United Kingdom⁴⁶. Although physical inactivity (*i.e.*, not reaching current public health
181 guidelines) has not further increased in U.S. adults between 2001 and 2016⁴⁰, self-reported daily time
182 spent in SB (*i.e.*, too much sitting) increased from 5.7 hours in 2007-2008 to 6.4 hours in 2015-2016⁴⁷.
183 Accelerometry-derived data reported more than 8 daily hours spent in SB with an average of 8.2 daily
184 hours in the U.S.⁴⁸ and 8.8 hours in Europe⁴⁹. Thus, these changes in PA/SB have the potential to impact
185 TDEE and increase the risks of ill effects of SB.

186

187 1.3. Consequences of the reduction of habitual physical activity on total daily energy expenditure

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

191 about 65% of the TDEE of people living in the late Paleolithic Stone Age. Based on this estimate, they
192 wrote that our modern PAL is “below the level of physical exertion for which our genetically-determined
193 physiology and biochemistry have been programmed through evolution”. The same research group
194 further showed that modern hunter-gatherers had higher levels of PA than individuals living in the
195 modern U.S. They estimated that the difference was equivalent to walking 19 km per day for an adult
196 of 70kg, or 1,190 kcal/day⁵⁰. Leonard⁵¹ estimated that PAL was significantly lower in industrial as
197 compared to modern subsistence populations, reflecting a less active way of life. He calculated that
198 individuals living a subsistence lifestyle expended 411 kcal/day more than those living a modern
199 lifestyle. By comparison, following the American College of Sports Medicine (ACSM) PA
200 recommendations accounts for only 69 kcal/day, and 1 daily hour of intense exercise accounts for 330
201 kcal/day⁵². Egger et al.⁵³ compared EE in a group of actors paid to live like early Australian settlers to
202 that of a group of modern sedentary office workers. He estimated that activity levels were on average
203 1.6-fold lower in industrialized population than that of the forefathers from 150 years earlier. This was
204 equivalent to a difference of 8km/day of walking or about 380 kcal/day for a 70kg male.

205 Between 1950 and 2000, occupations associated with low intensity PA increased by more than 80%
206 while those requiring high intensity PA declined by 25%⁴³. It has been estimated that these changes
207 resulted in a decrease in work related EE of 130 kcal/day over 50 years⁵⁴. Some studies suggest this drop
208 in occupational PA was offset by an increase in PA during leisure time⁴³. However, other studies found
209 that leisure PA only increased by 0.5% per year in Australian males between 1989 and 2011⁵⁵. It was
210 also estimated that leisure-time PA slightly increased in U.S. adults between the 1990’s and the 2000’s
211 associated with a substantial decline in household, work and transport-related activities⁴³. Although
212 informative, all these data have to be taken with caution given they were self-reported. It is only from
213 the 2000’s that the objective measurement of daily PA patterns has become common with the
214 development and growing availability of reliable activity monitors⁵⁶.

215

216 Taken together, these studies suggest that there has been a major drop in PA over the millennia with a
217 hypothetical average EE about 400-1,100 kcal/day greater in early *Homo Sapiens* compared to the
218 modern “*Homo Sedentarius*” who suffers from “diseases of civilization”³² (**Figure 2**). Decreases in PA
219 and PA-related EE in high income societies have been reported in more recent years, from the 1950s-
220 1970s. On the other hand, data from NHANES showed an increase in EI of 168 and 335 kcal/day for
221 men and women, respectively between 1970 and 2000⁵⁷. These changes in PA and EI happened at a time
222 when the prevalence of obesity increased in the early 1980’s in the U.S. and Western Europe⁵⁸. Of note,
223 the chronic energy imbalance, or energy gap, (*i.e.*, difference between EI and EE) thought to be at the
224 origin of the obesity epidemic in the U.S. is only about 50-100 kcal/day⁵⁹. Although a parallel can be
225 made between the transition in PA and the global rise in overweight and obesity prevalence, some
226 objective data do not necessarily support a decline in TDEE over the past decades. When combining
227 data using gold standard doubly labelled water (DLW)-derived TDEE collected between the 1980’s and
228 early 2000’s, Westerterp & Speakman did not find any change in total or activity-related EE⁶⁰. These
229 observations and others have fed the debate on the role of PA in weight gain and its role in the obesity
230 epidemic. However, it is possible that changes in PA and TDEE or activity-related EE occurred before
231 the 1980’s. The impact of the changes in PA over time on TDEE therefore remains an open question.
232 Relationships between PA, SB and epidemiological measures of obesity can however bring valuable
233 insight on the influence of low levels of PA on body weight regulation (**Box 1**).

234 **- Please insert box 1 and figure 2 near here -**

235

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

237 **2.1. Associations from cross-sectional population studies**

238 Most, but not all cross-sectional studies have reported negative associations between PAL and measures
239 of obesity including body weight, body mass index (BMI), waist circumference and adiposity in adults
240 but also in adolescents and children⁶¹⁻⁶⁵. For example, data on almost 3,000 children and adolescents

241 assessed in the NHANES study showed that the least active group had the highest trunk fat mass⁶⁶.
242 Drenowatz et al.⁶⁷ observed in 430 adults (average age 27.7 y.o.) that the proportion of energy expended
243 in MVPA is lower in people with overweight than in those with normal weight. On a larger scale, Füzéki
244 et al.⁶⁸ reviewed the health benefits of LPA from the NHANES accelerometer dataset and included a
245 total of 37 studies conducted in adults (16 studies in a general adult population, 14 in adults with chronic
246 diseases, 9 in older adults and 1 in pregnant women). Eight studies showed negative associations
247 between time spent in LPA and waist circumference and four also reported negative associations with
248 BMI. A fifth study observed a negative association between LPA and waist circumference, but not with
249 BMI. The authors concluded that inactive people should engage in PA of any intensity, the duration of
250 the bouts being more important than intensity to protect against weight gain⁶⁸. A recent review from
251 Jakicic et al.⁶⁹ summarizing results from cross-sectional studies conducted in adults with overweight
252 and obesity concluded that BMI was inversely associated with total volume of MVPA when MVPA was
253 accumulated in bouts lasting more than 10 min. These data while suggestive of a relationship between
254 PA and obesity, do not allow definitive conclusions to be drawn.

255 Only a few studies have examined the associations between time spent in SB and body weight. Anjana
256 et al.⁷⁰ reported a negative relationship between self-reported sitting time and BMI and waist
257 circumference in 543 Indian adults. Martínez-González et al.⁷¹ conducted a survey in 15,239 men and
258 women >15 years of age living in the 15 member states of the European Union in 1999. They observed
259 independent associations between leisure-time PA, sitting time and body mass. More importantly,
260 sedentary time was positively associated with trunk fat, independent of time spent in MVPA.
261 Observational studies report that people who are overweight spend in general 2.5 hours/day sitting more
262 than people with normal weight, and they engage in bouts of SB that are of longer duration^{30,72}.
263 Conversely, people with normal weight interrupt prolonged sedentary periods with short bouts of PA
264 more often and spend more time in LPA than people who are overweight²².

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

267 likely to have higher body weight, BMI, adiposity and waist circumference. In contrast, active bouts
268 longer than 10 min, independent of the intensity (*i.e.*, LPA or MVPA), are positively associated with
269 less obesity⁶⁹. However, a correlation does not necessarily indicate causality. Do people with overweight
270 or obesity sit more and are less active because of the higher energy cost of moving their heavier body,
271 or do they weigh more because they sit more and are less active? The fact that habitual exercisers are
272 leaner than their inactive counterparts limits the interpretation of causality between PA and body weight
273 and composition. Potential confounding variables such as diet, habitual PA or maximal aerobic capacity
274 have also rarely been taken into account in these studies. Although observational and epidemiological
275 studies are informative, longitudinal studies provide better evidence regarding causality, and long-term
276 prospective randomized controlled trials (RCT) provide the best evidence on the relationships between
277 PA and weight.

278

279 2.2. Associations from longitudinal studies

280 A large number of studies has shown that people who are the most active gain the least weight over
281 time. In 2018, the Physical Activity Guidelines Advisory Committee⁷³ identified in a literature review
282 40 studies that assessed the relationship between PA and weight gain in adults over a follow-up period
283 ranging from 1 to 22 years. The authors reported strong evidence supporting relationships between
284 greater amounts of MVPA and attenuated weight gain in adults. A lack of long-term studies however
285 limited evidence to support a dose-response relationship with LPA. Observational studies also report
286 strong relationships between PA and prevention of long-term weight regain following weight loss. The
287 National Weight Control Registry (NWCR) is the largest prospective investigation of long-term
288 successful weight loss maintenance⁷⁴⁻⁷⁶ in more than 10,000 people who have lost at least 13.6 kg and
289 have kept the weight off for at least one year. Studies from the registry have shown that people who
290 have been successful with weight loss maintenance were people who maintain low EI and performed
291 high levels of PA⁷⁷. Most participants in the NWCR regularly engaged in structured PA⁷⁴⁻⁷⁶ and self-
292 reported one hour per day of MVPA⁷⁶, which exceeds the World Health Organization (WHO) physical

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

295 More recently, longitudinal studies have examined associations between sedentariness and weight
296 status. The CARDIA study⁷⁸ conducted in 1,826 adults (average age 45.4 y.o.) with overweight or
297 obesity observed that total and prolonged bouts of sedentary time (≥ 10 min) were directly associated
298 with BMI and waist circumference at baseline. After 5-year of follow-up, only prolonged sedentary
299 bouts at baseline, not total daily sedentary time, were associated with greater gain in BMI and waist
300 circumference⁷⁸. Results from the Nurses' Health Study cohort (1992-1998)⁷⁹ collected in 68,487
301 women aged between 30 and 55 y.o. showed that each additional 2 hours per day spent in TV viewing
302 increased obesity risk by 23% after a 6-year follow-up. Campbell et al.⁸⁰ conducted a meta-analysis on
303 23 prospective cohort studies in adults >18 y.o. from North America and Europe (follow-up ranging
304 from 1 to 21 years). They observed that the most sedentary individuals at baseline had a 1.33-fold higher
305 risk of developing overweight or obesity compared with the least sedentary individuals (mean difference
306 of 8 hours/day in SB between both groups). They estimated that an increment of 1 hour/day in SB was
307 associated with a significant (but not clinically relevant) 0.02 cm increase in waist circumference over
308 5 years. Nevertheless, the authors found inconsistent and non-significant associations between SB at
309 baseline and other measures of obesity due to a high degree of heterogeneity in the data. Twenty one
310 studies out of the 23 included in this review used questionnaires to assess SB, which are known to
311 overestimate PA and underestimate SB^{41,81}; while only two used accelerometry-derived data for
312 assessing daily time spent in SB. To identify the determinants of longitudinal weight gain, a recent
313 clinical trial examined associations between metabolic and behavioral responses to short-term
314 overfeeding and 5-year changes in body mass and composition in adults with normal weight. Individuals
315 who reduced their objectively measured sedentary time the least following a 3-day overfeeding period
316 were those who gained the most body and fat mass over 5 years of observation. Of note, no association
317 was observed between the changes in total calorie intake, TDEE, or daily time spent in MVPA and LPA

318 in response to the acute overnutrition and longitudinal weight gain⁸². This finding supports a role for SB
319 in the regulation of body weight and adiposity.

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

324

325 2.3. Interventional studies

326 2.3.1. *Effect of changes in physical activity and sedentary behaviors on the prevention of* 327 *unhealthy weight gain*

328 The French ICAPS (Intervention Centered on Adolescents' Physical activity and Sedentary behavior)
329 study⁸³ aimed to both increase PA and reduce SB in 954 students (aged 11-12). This landmark socio-
330 ecological study relied upon a 4-year multi-level intervention that targeted the physical, organizational
331 (school, city) and social (teachers, peers, families) living environment of the children and the children
332 themselves through the synergistic actions of multiple partners. Compared to the control schools (no
333 intervention), pupils who received the intervention increased time spent in PA (-0.05 vs +0.90
334 hours/week, respectively), decreased sedentary time (-4.7 vs -19.9 min/day TV/video viewing,
335 respectively) and gained less weight throughout the 4 year-study (+0.41 kg/m² vs +0.10 kg/m² excess
336 BMI, respectively)⁸⁴. Importantly, the lifestyle changes induced by the intervention and the prevention
337 of weight gain were maintained 2.6 years after the end of the intervention with the highest efficacy in
338 the most sedentary and poorest adolescents⁸⁴. In a similar manner, the Dutch FATaintPHAT protocol⁸⁵
339 aimed to assess the efficacy of a computer-tailored program for adolescent students (aged 12-13)
340 targeting energy balance-related behaviors (*i.e.*, food intake and PA/SB). This 4-month cluster-
341 randomized trial included 20 schools with a 2-year follow-up. The intervention contributed to develop
342 knowledge on risk behaviors and favored intention towards changing these behaviors. The intervention

343 resulted in lower BMI and waist circumference at 2-years of follow-up in adolescents in the treatment
344 arm compared to those in the control group⁸⁵. The French ICAPS and the Dutch FATaintPHAT both
345 strongly support a role for SB reduction along with an increase in PA for preventing longitudinal weight
346 gain in children and adolescents. To our knowledge, no similar longitudinal study exists in adults or
347 elderly. Robust data from such studies are needed to support the role of PA in the primary prevention of
348 unhealthy weight in adults.

349

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

351 *2.3.2. Effect of changes in physical activity and sedentary behaviors on weight loss*

352 A general consensus is that exercise training (*i.e.*, MVPA) triggers physiological and behavioral
353 compensatory mechanisms that counteract the exercise-induced energy deficit and lead to only a modest
354 weight loss (1-2kg)¹⁰. Exercise training is therefore generally not considered to be an effective tool to
355 produce weight loss. Yet, clinically relevant weight loss can be achieved if training is above PA
356 recommendations, daily practiced and/or performed under supervision⁸⁶⁻⁸⁸. In the Midwest Exercise
357 Trial (MET) 2 study^{89,90}, adults with overweight or obesity lost on average 5% of their initial body
358 weight following a 10-month training with an expenditure of 400-600 kcal per supervised exercise
359 session 5 times a week. Nevertheless, high inter-individual variability was observed. Interestingly, those
360 who lost weight (*i.e.*, responders, >5% body weight loss) spontaneously decreased time spent in SB
361 during the 10-month intervention in favor of an increase in non-exercise PA (-27 min and + 39 min,
362 respectively); no change was observed in the daily PA pattern of non-responders (<5% initial body
363 weight). The E-MECHANIC study⁹¹ further showed that low levels of habitual MVPA and activity-
364 related EE are associated with less weight loss during a 24-week exercise intervention in adults with
365 overweight or obesity. In the Step-Up study⁹², an 18-month behavioral weight loss intervention that
366 combined calorie restriction and PA in adults with overweight or obesity (aged 18-55) the individuals
367 who lost more than 10% of initial body weight spent more time in prolonged bouts (>10 min) of both

368 MVPA and LPA. Secondary analyses of large intervention studies in adults with overweight or obesity
369 involved in the Diabetes Prevention Program (DPP) or Look AHEAD study also suggested that
370 decreasing SB, particularly of long duration and replacing sedentary time with MVPA, is associated
371 with weight loss⁹³. Furthermore, while interventions based on low volumes of exercise training did not
372 produce much weight loss⁹⁴⁻⁹⁶, training above the current PA recommendations (225-420 min/week of
373 exercise or MVPA) have shown more success⁹⁷. However, other studies showed that high volume of
374 additional PA can induce concomitant decreases in non-exercise PA and increases in SB, especially in
375 people with overweight or obesity⁹⁸⁻¹⁰⁰ and low levels of habitual PA⁹¹. The factors triggering the
376 spontaneous behavioral compensations and the associated inter-individual variability are however still
377 unclear.

378 The commonly observed compensatory decreases in LPA in response to high volumes of MVPA may
379 result from the difficulty that sedentary-inactive people encounter when performing unusual and/or new
380 activities of moderate-to vigorous intensity. For those individuals, increasing LPA may be a reasonable
381 alternative to increase total PA time¹⁰¹. Because LPA represents the most variable component of
382 TDEE¹⁰², it has the potential to influence energy balance and hence, body weight. For example, the study
383 from Holliday et al.²¹ compared the effect of two interventions: one targeting LPA through increases in
384 daily PA and another targeting MVPA (5 sessions per week of 30 min/day). The first intervention
385 promoting participation in daily life activities resulted in higher daily time spent in LPA, lower sedentary
386 time and greater android fat loss after 24 weeks compared to what was observed in the group assigned
387 to the structured MVPA program. Of note, while the time spent in PA of different activities varied
388 between the two groups at the end of the intervention, the total daily active time was not different. This
389 study supports the promotion of activities of daily living as an efficient strategy to increase total PA,
390 reduce body mass and improve adiposity. More recently, Swift et al.¹⁰³ observed that the combination
391 of an aerobic exercise protocol with increases in daily steps (to avoid sedentariness) in adults with
392 obesity was more effective than a protocol based on aerobic exercise alone in decreasing waist
393 circumference (-4.7 vs -2.1 cm, respectively), body weight (-4.1kg or -3.5% vs -1.7kg or -1.8%,

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

397 Another approach is to target SB in addition to PA^{104,105}. Fanning et al.¹⁰⁶ conducted a study of adding
398 structured aerobic exercise of moderate intensity 200 min/week to a dietary weight loss program with
399 or without advice to "sit less" in individuals with obesity (aged 65-85) involved in a 6-month supervised
400 protocol. They found that the addition of the structured exercise intervention did not produce more
401 weight loss than the combined weight loss and sit less program, nor the combination of weight loss, sit
402 less and structured exercise. This finding emphasizes the importance of sitting less before moving more.
403 In a systematic review and meta-analysis including data from 33 studies conducted in adults with normal
404 weight or overweight (BMI 22.1 to 35.9 kg/m²), Hadgraft et al.¹⁰⁴ reported a small but significant effect
405 of interventions aiming to reduce SB (2 weeks to <6 months) on body weight (-0.56 kg), waist
406 circumference (-0.72cm) and percent body fat (-0.26%). Another meta-analysis including 18 studies of
407 adults with metabolic disorders such as overweight/obesity or type II diabetes, cardiovascular and
408 musculoskeletal diseases¹⁰⁵ reported that a reduction of 64 min/day in sedentary time was associated
409 with decreased body fat (-0.66%) and waist circumference (-1.52 cm). In another systematic review and
410 meta-analysis of 9 studies in adults with both normal weight and overweight (aged 45.3), Saeidifard et
411 al.¹⁰⁷ concluded that replacing sedentary time with standing (+1.33 hours/day) was associated with
412 reductions on body fat mass (-0.75 kg). These studies show that reducing sedentary time can promote
413 weight loss. While these effects appear to be minor to moderate at an individual level, they could be
414 beneficial at the population level and therefore be relevant from a public health perspective.

415

416 *2.3.3. Effect of changes in physical activity and sedentary behaviors on weight loss maintenance*

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

419 results. Several RCTs that examined the effects of increases in PA on weight loss maintenance in adults
420 did not show protective effects of MVPA against weight regain following weight loss¹⁰⁸⁻¹¹⁷. By contrast,
421 Fanning et al.¹⁰⁶ found that body and fat mass regains 18 months after the cessation of a 6-month PA
422 intervention were significantly lower in an intervention combining dietary restriction, an exercise
423 program and advice to sit less when compared to the dietary restriction and structured exercise only arm.
424 These differences were linked with greater total active time in the daylong movement intervention due
425 to greater time spent in LPA, confirming the importance of moving throughout the day for weight
426 management. More RCTs with interventions targeting both PA and SB and a tight monitoring of daily
427 activities are needed to better understand the role of PA in weight loss maintenance.

428

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

439

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

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

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

450

451 3.1. Effect of changes in physical and sedentary activities on energy expenditure

452 3.1.1. *In adults with normal weight or overweight*

453 Total daily EE is defined as the sum of resting metabolic rate, diet-induced thermogenesis and activity-
454 related EE (exercise and volitional activities). Theoretically, an increase in PA should lead to an increase
455 in TDEE. Yet, spontaneous compensatory behavioral and physiological mechanisms seem to be
456 recruited when PA increases¹¹⁸. Rowland⁸ and Pontzer et al.⁹ have argued that an increase in exercise-
457 induced EE is compensated, at least above a certain level, by a decrease in non-exercise-induced EE,
458 thus leading to a plateau in TDEE. When pooling data from the 2,500 adults from the Modeling the
459 Epidemiological Transition Study (METS) cohort¹¹⁹, the authors assessed the relationship between
460 TDEE measured with DLW adjusted for sex and anthropometric parameters and PA measured by
461 accelerometry. Analyses showed a change point (*i.e.*, the activity level at which the slope of the change-
462 point regression becomes indistinguishable from zero) around 230 counts per minute per day
463 (CPM/day), which was estimated by the authors to an approximate TDEE of 2,600 kcal/day¹¹⁹.

464 To better understand the impact of increases in PA on TDEE in non-elite athletes, **table 1** summarizes
465 a non-exhaustive list of studies during which free-living TDEE was assessed with the DLW method
466 before and after an exercise protocol intervention. Overall, results reveal a great deal of heterogeneity.
467 While some studies observed an increase in total EE after an exercise intervention⁹⁰, others did not¹²⁰⁻
468 ¹²². For example, the MET 2 study conducted in adults with overweight or obesity reported increases of

469 310 kcal/day in TDEE in responders (body weight loss >5% from baseline) after 10 months of
470 supervised exercise 5 days/week with a controlled EE of 400 kcal or 600 kcal per exercise session (2,000
471 or 3,000 kcal/week)⁹⁰. In a 2-month intervention consisting of moderate intensity aerobic exercise
472 conducted in sedentary men with overweight or obesity, Lefai et al.¹⁰⁰ observed no change in total or
473 activity-related EE due to a spontaneous decrease in non-training activity-related EE, associated with
474 reduced time spent in LPA. This lack of change is consistent with the constrained TDEE theory⁹ as their
475 TDEE may have been close to a threshold value (3,368 kcal/day at baseline). However, in the same
476 study the authors observed a significant increase in both activity and TDEE in sedentary male with
477 normal weight adults after the same 2-month intervention on PA¹⁰⁰, with an increase from 2,556 kcal/day
478 at baseline to 2,938 after the intervention. Whybrow et al.¹²³ observed that young healthy individuals
479 performing 40 min sessions on stationary bicycle targeting 3.3 kcal/kg of body weight for 16 days
480 increased their TDEE to 3,272 kcal/day through exercise-induced EE. However, no change in body or
481 fat mass was observed. In this study, subjects compensated for about 30% of the exercise-induced energy
482 deficit by increasing EI. Nevertheless, a high degree of variability in compensation among individuals
483 was reported by the authors. Indeed, several factors may influence the degree of energy compensation.

484 Recently, the International Atomic Energy Agency (IAEA) DLW database group combined data of
485 DLW-derived TDEE in 1,754 adults and showed that adiposity has a strong association with the degree
486 of compensation associated with PA through decreases in other components of TDEE¹²⁴. People in the
487 10th percentile of BMI distribution compensate 27.7% of activity calories vs 49.2% for people in the 90th
488 percentile. In other words, only 72.3% and 50.8% of additional activity-related EE actually translate
489 into extra energy consumed during the day for the 10th and 90th percentile of BMI, respectively. That
490 means that individuals with higher fat levels compensate more for energy expended in PA than those
491 with lower adiposity. This goes along with the findings of the longitudinal PA intervention study
492 conducted by Lefai et al.¹⁰⁰ and reported above. The recent study by Willis et al.¹²⁵ examined the
493 relationship between PA and TDEE objectively measured in 584 older adults (aged 50-74) over a 6-
494 month period. Their findings suggest that energy balance status, estimated based on the 6-month changes

495 in body mass, plays an important role in the degree of compensation for energy expended in PA. They
496 showed that TDEE (adjusted on sex, ethnical and anthropometric parameters) increased with deciles of
497 objectively-measured PA by 705 and 430 kcal/day between the bottom and top deciles for individuals
498 in stable and positive energy balance (*i.e.*, with stable or higher body mass over 6 months compared to
499 baseline, respectively). No difference was observed in individuals in negative energy balance (*i.e.*, lower
500 body mass over 6 months compared to baseline) given that only a slight decrease of 56 kcal/day was
501 observed between people at the bottom and the top deciles of PA. Goran et al.¹²² however observed that
502 elderly people (aged 56-78) maintained stable TDEE after an 8-week endurance training intervention at
503 60-85% VO₂max (from 2,408 kcal/day at baseline to 2,474 kcal/day after 8 weeks of intervention). No
504 change in body mass or fat mass was observed. The terms (volume, intensity, frequency and duration)
505 of PA training also seem to influence the impact of PA on TDEE and body weight. Riou et al.⁹⁹ compared
506 the effect of 3 months low vs moderate intensity exercise training on EI, TDEE, time spent in LPA and
507 SB and body weight. The two trainings were matched to induce similar extra EE of 1500 kcal/week.
508 None of the PA intervention impacted EI and TDEE; a non-significant decrease in TDEE was observed
509 in the moderate-intensity exercise training group (-173 kcal/day). However, participants in the moderate-
510 intensity training group elicited greater reduction in daily walking time and higher increase in time spent
511 lying down than participants in the low-intensity training group. These spontaneous behavioral
512 adaptations indicate more pronounced energy compensation following moderate-intensity training
513 compared to a low intensity exercise training protocol (161 vs 49% of the exercise-induced EE). These
514 behavioral and energetic differences translated into about 1kg weight gain in the moderate-intensity
515 training group vs 1kg weight loss in the low-intensity training group. Flack et al.¹²⁶ recently compared
516 the metabolic effect of a 12-week aerobic training intervention consisting of 6 sessions per week of 40-
517 60 min at 50-59 % heart rate reserve exercise to a calorie and intensity-matched training program
518 consisting of 2 sessions per week of 90-120 min exercising in adults with overweight or obesity. Those
519 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
520 2 sessions per week group maintained stable body and fat mass. Interestingly, individuals in the 6
521 days/week group expended 85 kcal/day more than their counterparts. The total daily amount of exercise-

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

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

528

529 Altogether these studies suggest that 1) increases in PA can raise TDEE above the hypothesized plateau
530 of 2,600 kcal/day proposed by some research groups, at least in response to short/medium term
531 interventions, 2) the modalities of PA training likely influence the propensity to compensate for exercise
532 training EE, and 3) the impact of increases in PA on TDEE may depend on individual characteristics,
533 *i.e.*, adiposity, habitual EE, age, energy balance status, and other factors. An important point that remains
534 unknown is whether the behavioral and physiological compensatory mechanisms develop as people put
535 on weight or whether compensations are a “pre-existing” condition as described in the “thrifty gene”
536 theory¹²⁷. In other words, do people accumulate fat mass because they compensate more, or do they
537 compensate more because they have greater adiposity?

538

539 *3.1.2. In adults with reduced weight*

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

547 1.55 for the successful weight loss maintainers, individuals with normal weight, and those with obesity,
548 respectively). Furthermore, the weight loss maintainers, like the individuals with normal weight, spent
549 more time in LPA and less in SB than people with obesity, but also spent more time in MVPA than both
550 other groups. This study suggests that maintaining weight loss over the long term is associated with high
551 levels of both LPA and MVPA and reduced sedentary time. It further supports previous findings
552 indicating that a minimum PAL of 1.7-1.8 is required to prevent excessive weight regain.

553

554 In 2003, experts at a consensus meeting were already suggesting that moderate intensity activity of
555 approximately 45-60 minutes per day, or 1.7 PAL, was likely sufficient to prevent the transition to
556 overweight or obesity, and 60-90 minutes of moderate intensity activity, or 1.8 PAL, were required to
557 prevent weight regain in individuals with former obesity¹⁴. Regardless the exact PAL value, it is
558 substantially below the maximal sustainable PAL of 3.5 described by Thurber et al.¹². The same is true
559 for the PAL of the general population (i.e., 1.7-1.8)¹³, which is much lower than the hypothetical
560 maximal values. Therefore, the constrained energy model does not exclude a major role of PA in body
561 weight regulation, and future longitudinal studies are needed to clarify the relationships between PA/SB
562 and TDEE. However, focusing our attention on TDEE only, without considering the direct and indirect
563 effects on EI would be misleading. It is only by integrating the effects of PA/SB on both sides of the
564 energy balance equation that we will be able to fully understand their respective effects on the regulation
565 of body mass and composition.

566

567 3.2. Effect of changes in physical and sedentary activities on energy intake

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

572 requirements and led to weight gain¹³⁰. EI being mediated by appetite signals, various studies suggest a
573 “J-shaped curve” between the whole spectrum of PA (*i.e.*, from very low to very high level) and appetite
574 regulation^{57,130,131}. Hedonic and behavioral systems regulating EI may be altered in environments where
575 food is consumed in excess. These dysregulations may overpower biologic systems¹³² and amplify the
576 disequilibrium of energy balance.

577 The concept of “energy flux”, defined as “the magnitude of total energy turnover while maintaining
578 energy balance over periods of weeks to months”¹¹, can help us better understanding these different
579 observations. This concept suggests that increasing PA would allow higher EI to balance higher EE in
580 a state of high energy flux. When compared with a state of low energy flux, high energy flux may better
581 regulate weight and fat gain and limit weight regain^{10,11}. This approach might be more sustainable than
582 decreasing EI to match low PA over prolonged periods of time. However, the way energy is expended
583 should be considered, rather than just TDEE¹¹. Shook et al.¹³³ conducted a 1-year follow up in 421 male
584 adults with normal weight. The authors observed higher weight gain in the least active people compared
585 to their most active counterparts. This was partly explained by an incapacity to reduce EI during the
586 period of reduced PA, potentially due to a failure to generate or respond to satiety signals¹³⁴. While SB
587 should be taken into account in the complex relationship between PA pattern and energy balance, its
588 characterization (*i.e.*, type of SB) should be specifically considered¹³⁵. Cross-sectional population
589 studies have shown associations between time spent in TV viewing or screening and unhealthy diet
590 habits (*i.e.*, higher consumption of energy-dense snacks and sugar-sweetened beverages, less fruit and
591 vegetables consumption) in children and adolescents^{136,137}. In an interventional study, Chaput et al.¹³⁸
592 observed that adolescents (average age 16.7 y.o.) spending 1-hour playing video games increased their
593 EE and EI compared with a resting alone condition, resulting in a 163 kcal-positive energy balance. The
594 same research group observed that EE was similar after a “knowledge-based work” task or a control
595 resting condition in 15 healthy adults women (average age 24.1 y.o.), while *ad-libitum* EI increased
596 leading to positive energy balance in the intervention group¹³⁸. Cognitively demanding tasks have been
597 shown to have different physiological consequences and energy sources than physically demanding

598 tasks. This might be explained by a higher glucose demand from the brain and the need to restore glucose
599 homeostasis, or an increased stress-induced cortisol secretion¹³⁵. Considering the context in which
600 physical and sedentary activities are performed remains an understudied area and further research is
601 needed. This is particularly important to better understand the overall impact of the technological and
602 digital revolutions that have drastically modified our work and lifestyles.

603 In contrast to SB, high levels of PA improve homeostatic control of appetite in response to acute
604 disturbances¹³⁹. Stubbs et al.¹³⁴ observed that being moderately active provided better regulation of food
605 intake than being sedentary following *ad libitum* meal, despite no change in hunger, appetite or weight.
606 Myers et al.¹⁴⁰ reported negative associations between disinhibition and binge eating and both LPA and
607 MVPA (assessed during one week in free-living conditions with accelerometers) in people with
608 overweight or obesity. They further observed that the most inactive individuals had higher fat mass, and
609 that fat mass was strongly correlated with appetite disorders suggesting a bidirectional relationship
610 between physical inactivity and obesity. Habitual activity seems to further influence the effect of
611 increases in PA. The E-MECHANIC trial that prescribed structured PA of 8 or 20 kcal/kg of body
612 weight per session during a 24-week intervention in adults with overweight or obesity showed that
613 habitual baseline MVPA levels, not the activity-related EE, predict changes in EI and body weight⁹¹. In
614 a recent cross-over randomized study¹⁴¹, we showed in lean healthy people that prolonged sitting (>30
615 minutes) was associated with greater food cravings before a meal compared to a day during which
616 sedentary activities were frequently interrupted by short bouts of moderate intensity PA, thus indirectly
617 supporting the adverse effect of SB on food intake control.

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

624

- Please insert box 3 near here -

625

626 Some studies suggest that food intake may be determined by lean body mass^{142,143}, especially under
627 energy deficit conditions during which the restoration of fat-free mass may become a priority for the
628 body. Others have shown that 24-hour EE is the major determinant of EI^{144,145}. Despite heterogeneity in
629 protocol modalities (*e.g.*, type of exercise, duration and intensity, chronicity, etc.), other data argue in
630 favor of a beneficial effect of PA on the appetite through hormones secretion in order to reach the
631 targeted “reference” weight¹⁴⁶. For example, Martins et al.¹⁴⁷ observed an improvement in appetite
632 control following 6 weeks of moderate exercise training in 29 healthy sedentary adults. King et al.¹⁴⁸
633 found that the increased fasting hunger following a 12-week exercise protocol in men and women with
634 overweight and obesity was accompanied by increased satiation following a fixed meal, partially
635 explained by an increase in anorexigenic hormones release, such as glucagon-like peptide 1 (GLP1).
636 Flack et al.¹²⁶ reported in participants with overweight or obesity that greater reductions in postprandial
637 leptin concentration following a 12-week exercise intervention were associated with lower energy
638 compensation (difference between estimated and actual changes in body composition). The authors
639 suggested that reductions in the levels of postprandial leptin indicate an improvement in leptin sensitivity
640 with exercise training which helps controlling food intake. During a two-month bedrest study¹⁴⁹, a model
641 that induces extreme levels of physical inactivity and sedentariness, we observed that lean healthy active
642 women were able to adjust their EI to the very low levels of PA, and that fasting leptin was negatively
643 associated with spontaneous EI, thus also suggesting some relationships between PA, leptin and food
644 intake. The mechanisms underlying the relationships between PA and food intake still warrant further
645 investigations though.

646

647 3.3. The protective effects of physical activity against overfeeding

648 It has been suggested that overfeeding might trigger adaptive physiological responses to dissipate excess
649 energy in order to achieve energy balance and maintain a stable weight by increasing TDEE. Levine et
650 al.²⁰ observed that following 8 weeks of over-nutrition in adults with normal weight, those that
651 spontaneously increased their PA the most gained the least amount of body fat. An early study by
652 Ravussin et al.¹⁵⁰ found an increase in TDEE following 9 days of overfeeding of which one third was
653 explained by increased basal metabolic rate. However, only 25% of the excess energy consumed was
654 dissipated through an increased EE, the other portion being stored in the body. More recently, Johannsen
655 et al.¹⁵¹ conducted a longer overfeeding protocol (8 weeks) and found a significant increase in TDEE
656 driven by an increase in sleeping metabolic rate. Even if this increase was statistically significantly,
657 from a clinical point of view it was insufficient to prevent weight gain. Long-term overfeeding studies
658 described an increase in body weight that was slowing down as the intervention was sustained over
659 several months, likely due to increases in both resting metabolic rate and energy costs to move a heavier
660 body¹⁵². None of these studies observed increasing levels of PA thought to be protective against weight
661 gain like it was initially suggested in the study by Levine et al.²⁰ Finally, the existence and magnitude
662 of these adaptations are still debated¹⁵¹ in part due to the large inter-individual variability observed in
663 these studies¹⁵². Results suggest that the dynamic processes that maintain stability of energy balance
664 over time (*i.e.*, simultaneous increase or decrease in EE with increases or decreases in EI) are complex
665 and need further investigation (**Figure 3**).

666 **- Please insert figure 3 near here -**

667

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

669 In addition to a stable energy balance, a second condition is required for the maintenance of a stable
670 body weight: stable oxidative balances. This means the amounts of substrates consumed by the body
671 need to be oxidized. As elegantly explained by the two-compartment model of Jean-Pierre Flatt¹⁵³,
672 oxidative balance is influenced by the capacity to store each macronutrient in the body. Proteins

673 being required for the structure, function, and regulation of the body's tissues and organs, their balance
674 is tightly regulated by the organism. Because the storage of carbohydrates (CHO) is limited to few
675 hundred grams essentially in skeletal muscles and the liver, changes in CHO intakes induce large
676 variations in the level of the glycogen stores which are rapidly adjusted by their oxidation. Conversely,
677 changes in fat intake cause only small variations in the level of the large stores of fat in the body and are
678 not followed by equivalent changes in lipid oxidation. Fat balance has been shown to be tightly linked
679 to energy balance and plays an important role in body mass and composition management¹⁵⁴.

680 By lowering glycogen stores, exercise can promote fat oxidation¹⁵⁴. By contrast, low levels of PA reduce
681 the ability of the body to use lipids as substrates for meeting energy needs¹⁵⁵, and promote the
682 development of metabolic inflexibility (*i.e.*, incapacity for an organism to adjust fuel oxidation to
683 changes in fuel availability^{156,157}). The concept of metabolic flexibility implies that metabolic health is
684 determined by the ability to adapt to conditions of temporary stress, such as overfeeding or exercise, and
685 thus maintain or regain homeostasis. Previous studies have shown that activity-related EE, but not
686 TDEE, predicts nutrient partitioning¹⁵⁸ and metabolic flexibility¹⁵⁹⁻¹⁶¹. Importantly, these associations
687 between activity-related EE, nutrient partitioning and metabolic flexibility were observed independent
688 of detectable changes in energy balance, and even in the absence of an increase in TDEE¹⁰⁰. Finally, it
689 has been shown that the inability to both decrease time spent sedentary and adjust fuel use (metabolic
690 inflexibility) to an acute overfeeding episode was correlated with long-term weight gain^{82,162}. Altogether,
691 these studies suggest key roles for PA, SB and activity-related EE in the regulation of oxidative balance
692 and metabolic flexibility, two key factors involved in the regulation of body weight¹⁶¹ (**Box 4**).

693 **Please insert box 4 near here -**

694

695 **Conclusion & future directions**

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

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

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

- 723 - Consider and objectively measure daily LPA and SB.

- 724 - Consider that the role of PA in the primary prevention of weight gain may differ from its role
725 in the prevention of weight regain after weight loss. In the context of weight gain, PA is an
726 environmental factor that contributes to induce a positive energy balance when low levels of PA
727 are not matched by low levels of EI. Following weight loss, PA is now rather a tool to combat
728 the biological mechanisms that are driving weight regain. The role of PA in these two distinct
729 biological contexts require specific research; yet studies in people who have lost weight are still
730 missing.
- 731 - Dissociate PA and PA-related EE. Although these two are closely related, PA refers to behaviors
732 and body movements, and PA-related EE corresponds to the metabolic cost associated with PA.
733 Measuring PA-related EE objectively requires combining the DLW method and indirect
734 calorimetry. Raw data (*i.e.*, unadjusted) of PA-related EE should no longer be presented as it is
735 prone to misinterpretation. While an adult with overweight can have PA-related EE as high as
736 an adult with normal weight, the former results from the high cost of moving a large body while
737 the latter is explained by high levels of daily PA. Data adjusted for body mass/composition
738 should be presented in the future.
- 739 - Conduct adequately-powered RCTs to examine the influence of PA/SB on weight regulation.
740 These studies should consider potential confounding variables such as habitual PA, maximal
741 aerobic capacity, the type of PA and SB performed, the context in which the physical and
742 sedentary behaviors are undertaken, food intake habits, sleep pattern, sex, etc.
- 743 - Consider interdisciplinary approaches that will aim to determine the relative contribution of the
744 environmental, socio-ecological and biological factors in body weight regulation. As we
745 recently discussed it in a viewpoint³⁷, studying populations that have maintained a pre-industrial
746 lifestyle and are facing rapid and drastic environmental changes due to modernization may help
747 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.

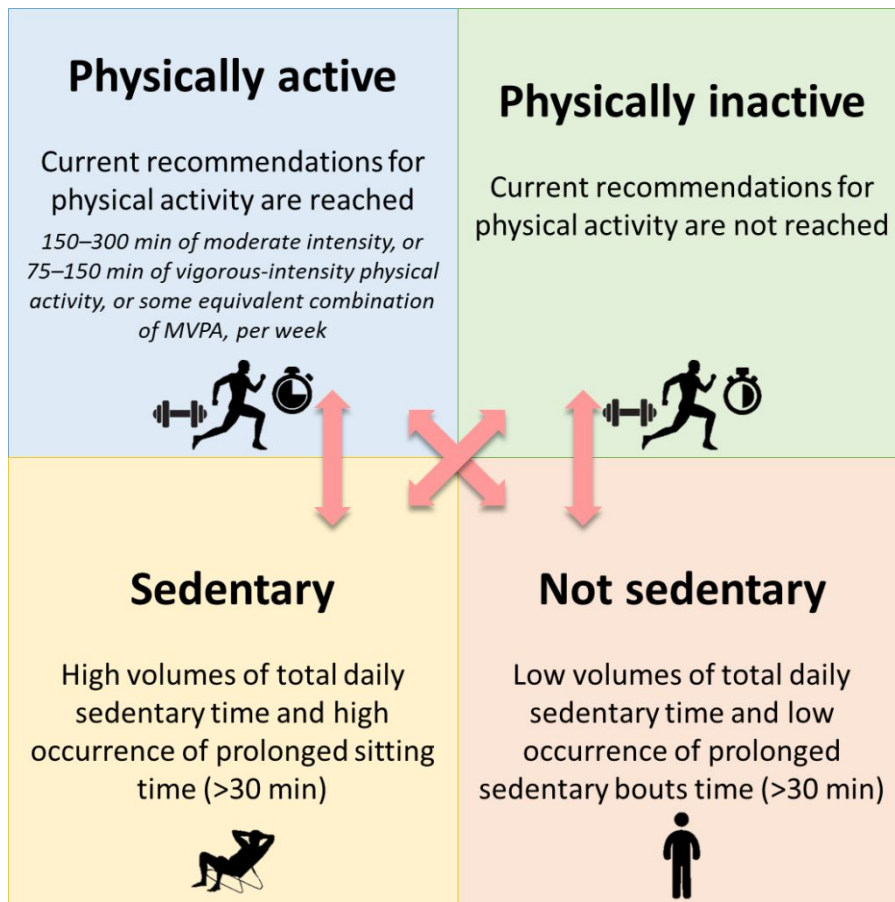
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754 **Figures**

755 Figure 1:

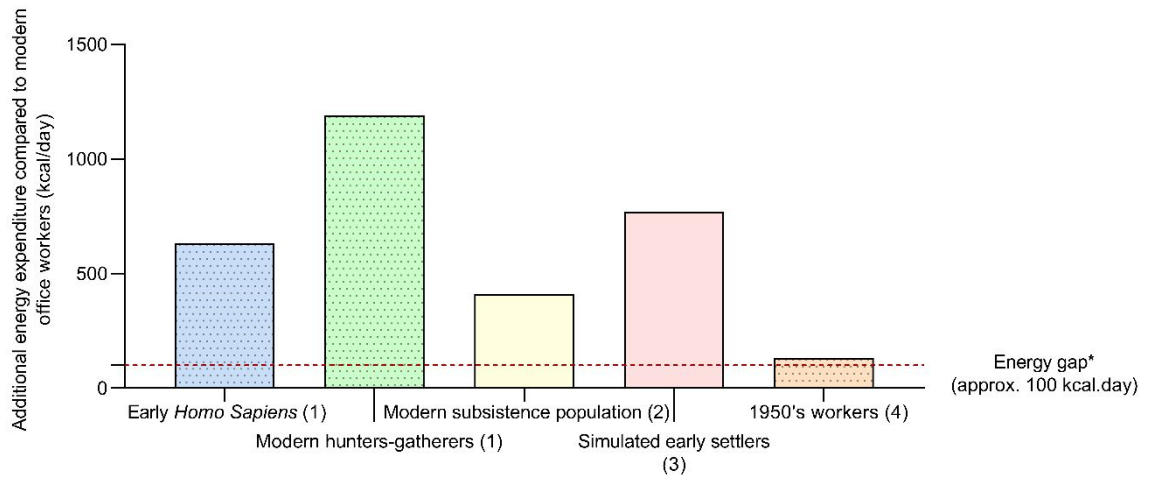


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759 Figure 2

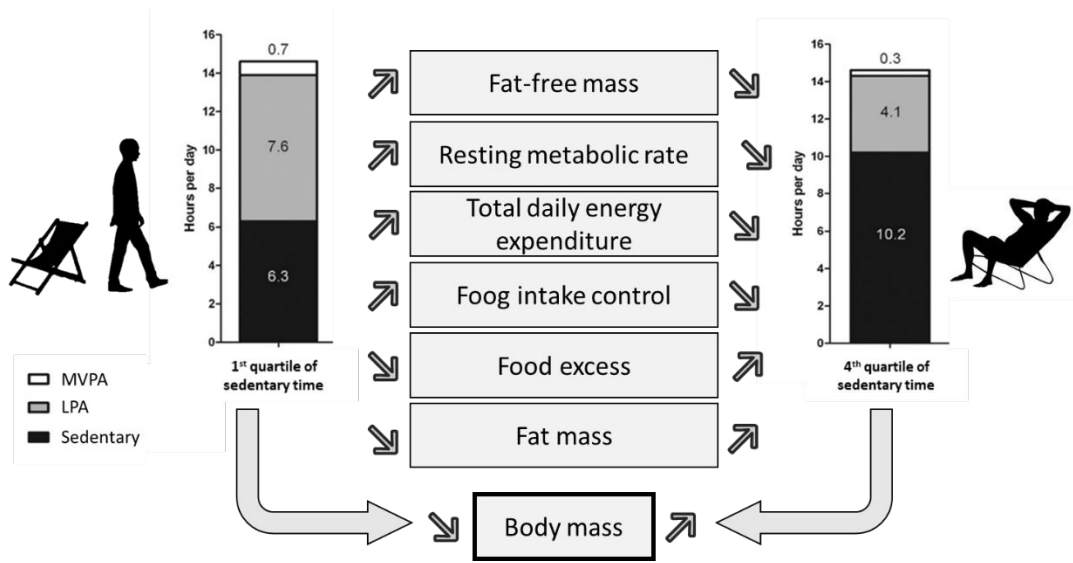


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763 Figure 3:



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766

767 **Figures legend**

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

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

772

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

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

781

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

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

787

788

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**

792

Author	Year	Population	Intervention	Changes in total daily energy expenditure	Changes in obesity markers	Differences between group
Goran et al. ¹²²	1992	6M (age: 68 (SD 7) y.o.; BMI: 24.9 (2.3) kg/m ²)	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 ²)	No control group		FM: from 21.58 (6.64) to 20.68 (6.61) kg	
Herrmann et al. ⁹⁰	2015	31 M / 31 W (age: 22.6 (SD 4.2) y.o.; BMI: 31.2 (4.8) kg/m ²)	6 months of aerobic training targeting 400 or 600 kcal/week	<i>Responders</i> ^a : from 2,866 (SD 598) to 3,137 (658) kcal/d	<i>Responders</i> ^a : 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 ^{a, b}		<i>Non-responders</i> ^b : from 3,000±737 to 3,169±675 kcal/day	<i>Non-responders</i> ^b : BM: -0.04 (2.5) %	
Hunter et al. ¹²⁰	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 ²)	<i>Aerobic</i> : 3-5 times/week during 8 weeks treadmill walking / jogging (20 to 40 min at 67 to 80% HR _{max})	<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 ²)	<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 ²)	All subjects were provided an 800-kcal diet until reach a BMI <25 kg/m ²	<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. ¹⁶⁵	2017	<i>Lower dose</i> : 37 W (age: 65.7 (SD 4.5) y.o.; BMI: 25.5 (3.9) kg/m ²) <i>Higher dose</i> : 35 W (age 65.2 (4.1) y.o.; BMI: 25.8 (3.0) kg/m ²)	Walking protocol at 50-55% HR _{reserve} 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

^a: 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

^b: 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).

796 **References**

- 797 1. Luke A, Cooper RS. Physical activity does not influence obesity risk: time to clarify the public
798 health message. *Int J Epidemiol*. Dec 2013;42(6):1831-6. doi:10.1093/ije/dyt159
- 799 2. Blair SN, Archer E, Hand GA. Commentary: Luke and Cooper are wrong: physical activity has
800 a crucial role in weight management and determinants of obesity. *Int J Epidemiol*. Dec 2013;42(6):1836-
801 8. doi:10.1093/ije/dyt160
- 802 3. Swinburn B. Commentary: physical activity as a minor player in the obesity epidemic: what are
803 the deep implications? *Int J Epidemiol*. Dec 2013;42(6):1838-40. doi:10.1093/ije/dyt162
- 804 4. Hill JO, Peters JC. Commentary: physical activity and weight control. *Int J Epidemiol*. Dec
805 2013;42(6):1840-2. doi:10.1093/ije/dyt161
- 806 5. Wareham NJ, Brage S. Commentary: Physical activity and obesity; scientific uncertainty and
807 the art of public health messaging. *International Journal of Epidemiology*. 2014;42(6):1843-1845.
808 doi:10.1093/ije/dyt164
- 809 6. Fisher G, Hunter GR, Allison DB. Commentary: physical activity does influence obesity risk
810 when it actually occurs in sufficient amount. *Int J Epidemiol*. Dec 2013;42(6):1845-8.
811 doi:10.1093/ije/dyt163
- 812 10.1093/ije/dyt163.
- 813 7. Luke A, Cooper RS. Authors' response to commentaries on 'Physical activity does not influence
814 obesity risk'. *International Journal of Epidemiology*. 2014;42(6):1848-1851. doi:10.1093/ije/dyt171
- 815 8. Rowland TW. The biological basis of physical activity. *Med Sci Sports Exerc*. Mar
816 1998;30(3):392-9. doi:10.1097/00005768-199803000-00009
- 817 9. Pontzer H. Constrained Total Energy Expenditure and the Evolutionary Biology of Energy
818 Balance. *Exerc Sport Sci Rev*. Jul 2015;43(3):110-6. doi:10.1249/JES.0000000000000048
- 819 10. Foright RM, Presby DM, Sherk VD, et al. Is regular exercise an effective strategy for weight
820 loss maintenance? *Physiol Behav*. May 1 2018;188:86-93. doi:10.1016/j.physbeh.2018.01.025
- 821 11. Melby CL, Paris HL, Sayer RD, Bell C, Hill JO. Increasing Energy Flux to Maintain Diet-
822 Induced Weight Loss. *Nutrients*. Oct 21 2019;11(10):2533. doi:10.3390/nu11102533
- 823 12. Thurber C, Dugas LR, Ocobock C, Carlson B, Speakman JR, Pontzer H. Extreme events reveal
824 an alimentary limit on sustained maximal human energy expenditure. *Sci Adv*. Jun 2019;5(6):eaaw0341.
825 doi:10.1126/sciadv.aaw0341
- 826 13. Westerterp KR, Yamada Y, Sagayama H, et al. Physical activity and fat-free mass during growth
827 and in later life. *Am J Clin Nutr*. Nov 8 2021;114(5):1583-1589. doi:10.1093/ajcn/nqab260
- 828 14. Saris WH, Blair SN, van Baak MA, et al. How much physical activity is enough to prevent
829 unhealthy weight gain? Outcome of the IASO 1st Stock Conference and consensus statement. *Obes Rev*.
830 May 2003;4(2):101-14. doi:10.1046/j.1467-789x.2003.00101.x
- 831 15. Schoeller DA, Shay K, Kushner RF. How much physical activity is needed to minimize weight
832 gain in previously obese women? *Am J Clin Nutr*. Sep 1997;66(3):551-6. doi:10.1093/ajcn/66.3.551
- 833 16. Weinsier RL, Hunter GR, Desmond RA, Byrne NM, Zuckerman PA, Darnell BE. Free-living
834 activity energy expenditure in women successful and unsuccessful at maintaining a normal body weight.
835 *Am J Clin Nutr*. Mar 2002;75(3):499-504. doi:10.1093/ajcn/75.3.499
- 836 17. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of
837 activity codes and MET intensities. *Med Sci Sports Exerc*. Sep 2000;32(9 Suppl):S498-504.
838 doi:10.1097/00005768-200009001-00009
- 839 18. Herzig KH, Ahola R, Leppaluoto J, Jokelainen J, Jamsa T, Keinanen-Kiukaanniemi S. Light
840 physical activity determined by a motion sensor decreases insulin resistance, improves lipid homeostasis
841 and reduces visceral fat in high-risk subjects: PreDiabEx study RCT. *Int J Obes (Lond)*. Aug
842 2014;38(8):1089-96. doi:10.1038/ijo.2013.224
- 843 19. Malaeb S, Perez-Leighton CE, Noble EE, Billington C. A "NEAT" Approach to Obesity
844 Prevention in the Modern Work Environment. *Workplace Health Saf*. Mar 2019;67(3):102-110.
845 doi:10.1177/2165079918790980

- 846 20. Levine JA, Eberhardt NL, Jensen MD. Role of nonexercise activity thermogenesis in resistance
847 to fat gain in humans. *Science*. Jan 8 1999;283(5399):212-4. doi:10.1126/science.283.5399.212
- 848 21. Holliday A, Burgin A, Fernandez EV, Fenton SAM, Thielecke F, Blannin AK. Points-based
849 physical activity: a novel approach to facilitate changes in body composition in inactive women with
850 overweight and obesity. *BMC Public Health*. Feb 17 2018;18(1):261. doi:10.1186/s12889-018-5125-2
- 851 22. Healy GN, Wijndaele K, Dunstan DW, et al. Objectively measured sedentary time, physical
852 activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Diabetes*
853 *Care*. Feb 2008;31(2):369-71. doi:10.2337/dc07-1795
- 854 23. Rantalainen T, Pesola AJ, Quittner M, Ridgers ND, Belavy DL. Are habitual runners physically
855 inactive? *J Sports Sci*. Aug 2018;36(16):1793-1800. doi:10.1080/02640414.2017.1420452
- 856 24. Thivel D, Duclos M. Inactive runners or sedentary active individuals? *J Sports Sci*. Jan
857 2019;37(1):1-2. doi:10.1080/02640414.2018.1477420
- 858 25. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical
859 activity and sedentary behaviour. *Br J Sports Med*. Dec 2020;54(24):1451-1462. doi:10.1136/bjsports-
860 2020-102955
- 861 26. Tremblay MS, Aubert S, Barnes JD, et al. Sedentary Behavior Research Network (SBRN) -
862 Terminology Consensus Project process and outcome. *Int J Behav Nutr Phys Act*. Jun 10 2017;14(1):75.
863 doi:10.1186/s12966-017-0525-8
- 864 27. Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the
865 United States, 2003-2004. *Am J Epidemiol*. Apr 1 2008;167(7):875-81. doi:10.1093/aje/kwm390
- 866 28. Ekelund U, Tarp J, Fagerland MW, et al. Joint associations of accelerometer measured physical
867 activity and sedentary time with all-cause mortality: a harmonised meta-analysis in more than 44 000
868 middle-aged and older individuals. *Br J Sports Med*. Dec 2020;54(24):1499-1506. doi:10.1136/bjsports-
869 2020-103270
- 870 29. Genin PM, Dessenne P, Finaud J, et al. Effect of Work-Related Sedentary Time on Overall
871 Health Profile in Active vs. Inactive Office Workers. *Front Public Health*. 2018 2018;6:279.
872 doi:10.3389/fpubh.2018.00279
- 873 30. Dunstan DW, Howard B, Healy GN, Owen N. Too much sitting - a health hazard. *Diabetes Res*
874 *Clin Pract*. Sep 2012;97(3):368-76. doi:10.1016/j.diabres.2012.05.020
- 875 31. Raichlen DA, Pontzer H, Zderic TW, et al. Sitting, squatting, and the evolutionary biology of
876 human inactivity. *Proc Natl Acad Sci U S A*. Mar 31 2020;117(13):7115-7121.
877 doi:10.1073/pnas.1911868117
- 878 32. Lightfoot JT. Why control activity? Evolutionary selection pressures affecting the development
879 of physical activity genetic and biological regulation. *Biomed Res Int*. 2013;2013:821678.
880 doi:10.1155/2013/821678
- 881 33. Steffen W, Persson A, Deutsch L, et al. The anthropocene: from global change to planetary
882 stewardship. *Ambio*. Nov 2011;40(7):739-61. doi:10.1007/s13280-011-0185-x
- 883 34. McLaughlin M, Atkin AJ, Starr L, et al. Worldwide surveillance of self-reported sitting time: a
884 scoping review. *Int J Behav Nutr Phys Act*. Sep 3 2020;17(1):111. doi:10.1186/s12966-020-01008-4
- 885 35. Dumith SC, Hallal PC, Reis RS, Kohl HW, 3rd. Worldwide prevalence of physical inactivity
886 and its association with human development index in 76 countries. *Prev Med*. Jul-Aug 2011;53(1-2):24-
887 8. doi:10.1016/j.ypmed.2011.02.017
- 888 36. Katzmarzyk PT, Friedenreich C, Shiroma EJ, Lee I-M. Physical inactivity and non-
889 communicable disease burden in low-income, middle-income and high-income countries. *British*
890 *Journal of Sports Medicine*. 2022;56(2):101-106. doi:10.1136/bjsports-2020-103640
- 891 37. Bourdier P, Duboz P, Macia E, et al. How interdisciplinary research at the crossroad between
892 socio-cultural anthropology, nutritional and physical activity physiology can help addressing the obesity
893 epidemic. *Cahiers de Nutrition et de Di t tique*. 2021;56(1):51-58. doi:10.1016/j.cnd.2020.11.003
- 894 38. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from
895 here? *Science*. Feb 7 2003;299(5608):853-5. doi:10.1126/science.1079857
- 896 39. Yegian AK, Heymsfield SB, Lieberman DE. Historical body temperature records as a
897 population-level 'thermometer' of physical activity in the United States. *Curr Biol*. Oct 25
898 2021;31(20):R1375-R1376. doi:10.1016/j.cub.2021.09.014

- 899 40. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity
900 from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants.
901 *Lancet Glob Health*. Oct 2018;6(10):e1077-e1086. doi:10.1016/S2214-109X(18)30357-7
- 902 41. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even
903 eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data
904 from more than 1 million men and women. *The Lancet*. 09/2016 2016;388(10051):1302-1310.
905 doi:10.1016/s0140-6736(16)30370-1
- 906 42. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the
907 United States measured by accelerometer. *Med Sci Sports Exerc*. Jan 2008;40(1):181-8.
908 doi:10.1249/mss.0b013e31815a51b3
- 909 43. Brownson RC, Boehmer TK, Luke DA. Declining rates of physical activity in the United States:
910 what are the contributors? *Annu Rev Public Health*. 2005 2005;26:421-43.
911 doi:10.1146/annurev.publhealth.26.021304.144437
- 912 44. Sturm R. Childhood obesity - what we can learn from existing data on societal trends, part 1.
913 *Prev Chronic Dis*. Jan 2005;2(1):A12.
- 914 45. De Jong NP, Debache I, Pan Z, et al. Breaking up Sedentary Time in Overweight/Obese Adults
915 on Work Days and Non-Work Days: Results from a Feasibility Study. *Int J Environ Res Public Health*.
916 Nov 16 2018;15(11)doi:10.3390/ijerph15112566
- 917 46. Ng SW, Popkin BM. Time use and physical activity: a shift away from movement across the
918 globe. *Obes Rev*. Aug 2012;13(8):659-80. doi:10.1111/j.1467-789X.2011.00982.x
- 919 47. Du Y, Liu B, Sun Y, Snetselaar LG, Wallace RB, Bao W. Trends in Adherence to the Physical
920 Activity Guidelines for Americans for Aerobic Activity and Time Spent on Sedentary Behavior Among
921 US Adults, 2007 to 2016. *JAMA Netw Open*. Jul 3 2019;2(7):e197597.
922 doi:10.1001/jamanetworkopen.2019.7597
- 923 48. Matthews CE, Keadle SK, Troiano RP, et al. Accelerometer-measured dose-response for
924 physical activity, sedentary time, and mortality in US adults. *Am J Clin Nutr*. Nov 2016;104(5):1424-
925 1432. doi:10.3945/ajcn.116.135129
- 926 49. Loyen A, Clarke-Cornwell AM, Anderssen SA, et al. Sedentary Time and Physical Activity
927 Surveillance Through Accelerometer Pooling in Four European Countries. *Sports Med*. Jul
928 2017;47(7):1421-1435. doi:10.1007/s40279-016-0658-y
- 929 50. Cordain L, Gotshall RW, Eaton SB, Eaton SB, 3rd. Physical activity, energy expenditure and
930 fitness: an evolutionary perspective. *Int J Sports Med*. Jul 1998;19(5):328-35. doi:10.1055/s-2007-
931 971926
- 932 51. Leonard WR. Size counts: evolutionary perspectives on physical activity and body size from
933 early hominids to modern humans. *J Phys Act Health*. Nov 2010;7 Suppl 3(s3):S284-98.
934 doi:10.1123/jpah.7.s3.s284
- 935 52. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated
936 recommendation for adults from the American College of Sports Medicine and the American Heart
937 Association. *Med Sci Sports Exerc*. Aug 2007;39(8):1423-34. doi:10.1249/mss.0b013e3180616b27
- 938 53. Egger GJ, Vogels N, Westerterp KR. Estimating historical changes in physical activity levels.
939 *Med J Aust*. Dec 3-17 2001;175(11-12):635-6. doi:10.5694/j.1326-5377.2001.tb143758.x
- 940 54. Church TS, Thomas DM, Tudor-Locke C, et al. Trends over 5 decades in U.S. occupation-
941 related physical activity and their associations with obesity. *PLoS One*. 2011 2011;6(5):e19657.
942 doi:10.1371/journal.pone.0019657
- 943 55. Chau J, Chey T, Burks-Young S, Engelen L, Bauman A. Trends in prevalence of leisure time
944 physical activity and inactivity: results from Australian National Health Surveys 1989 to 2011. *Aust N
945 Z J Public Health*. Dec 2017;41(6):617-624. doi:10.1111/1753-6405.12699
- 946 56. Troiano RP, McClain JJ, Brychta RJ, Chen KY. Evolution of accelerometer methods for
947 physical activity research. *Br J Sports Med*. Jul 2014;48(13):1019-23. doi:10.1136/bjsports-2014-
948 093546
- 949 57. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. *Circulation*. Jul 3 2012;126(1):126-
950 32. doi:10.1161/CIRCULATIONAHA.111.087213

- 951 58. Rodgers A, Woodward A, Swinburn B, Dietz WH. Prevalence trends tell us what did not
952 precipitate the US obesity epidemic. *The Lancet Public Health*. 2018;3(4):e162-e163.
953 doi:10.1016/s2468-2667(18)30021-5
- 954 59. Hill JO, Wyatt HR, Peters JC. The Importance of Energy Balance. *Eur Endocrinol*. Aug
955 2013;9(2):111-115. doi:10.17925/EE.2013.09.02.111
- 956 60. Westerterp KR, Speakman JR. Physical activity energy expenditure has not declined since the
957 1980s and matches energy expenditures of wild mammals. *Int J Obes (Lond)*. Aug 2008;32(8):1256-63.
958 doi:10.1038/ijo.2008.74
- 959 61. Ekelund U, Aman J, Yngve A, Renman C, Westerterp K, Sjostrom M. Physical activity but not
960 energy expenditure is reduced in obese adolescents: a case-control study. *Am J Clin Nutr*. Nov
961 2002;76(5):935-41. doi:10.1093/ajcn/76.5.935
- 962 62. Hunter GR, Kekes-Szabo T, Snyder SW, Nicholson C, Nyikos I, Berland L. Fat distribution,
963 physical activity, and cardiovascular risk factors. *Med Sci Sports Exerc*. Mar 1997;29(3):362-9.
964 doi:10.1097/00005768-199703000-00011
- 965 63. Hunter GR, Kekes-Szabo T, Truth MS, Williams MJ, Goran M, Pichon C. Intra-abdominal
966 adipose tissue, physical activity and cardiovascular risk in pre- and post-menopausal women. *Int J Obes
967 Relat Metab Disord*. Sep 1996;20(9):860-5.
- 968 64. Salbe AD, Fontvieille AM, Harper IT, Ravussin E. Low levels of physical activity in 5-year-old
969 children. *J Pediatr*. Sep 1997;131(3):423-9. doi:10.1016/s0022-3476(97)80069-8
- 970 65. Hallal PC, Reichert FF, Ekelund U, et al. Bidirectional cross-sectional and prospective
971 associations between physical activity and body composition in adolescence: birth cohort study. *J Sports
972 Sci*. 2012;30(2):183-90. doi:10.1080/02640414.2011.631570
- 973 66. Liao J, Cao C, Hur J, et al. Association of sedentary patterns with body fat distribution among
974 US children and adolescents: a population-based study. *Int J Obes (Lond)*. Sep 2021;45(9):2048-2057.
975 doi:10.1038/s41366-021-00874-7
- 976 67. Drenowatz C, Jakicic JM, Blair SN, Hand GA. Differences in correlates of energy balance in
977 normal weight, overweight and obese adults. *Obes Res Clin Pract*. Nov-Dec 2015;9(6):592-602.
978 doi:10.1016/j.orcp.2015.03.007
- 979 68. Fuzeki E, Engeroff T, Banzer W. Health Benefits of Light-Intensity Physical Activity: A
980 Systematic Review of Accelerometer Data of the National Health and Nutrition Examination Survey
981 (NHANES). *Sports Med*. Sep 2017;47(9):1769-1793. doi:10.1007/s40279-017-0724-0
- 982 69. Jakicic JM, Rogers RJ, Davis KK, Collins KA. Role of Physical Activity and Exercise in
983 Treating Patients with Overweight and Obesity. *Clin Chem*. Jan 2018;64(1):99-107.
984 doi:10.1373/clinchem.2017.272443
- 985 70. Anjana RM, Sudha V, Lakshmipriya N, et al. Reliability and validity of a new physical activity
986 questionnaire for India. *Int J Behav Nutr Phys Act*. Mar 18 2015;12:40. doi:10.1186/s12966-015-0196-
987 2
- 988 71. Martinez-Gonzalez MA, Martinez JA, Hu FB, Gibney MJ, Kearney J. Physical inactivity,
989 sedentary lifestyle and obesity in the European Union. *Int J Obes Relat Metab Disord*. Nov
990 1999;23(11):1192-201. doi:10.1038/sj.ijo.0801049
- 991 72. Johannsen DL, Welk GJ, Sharp RL, Flakoll PJ. Differences in daily energy expenditure in lean
992 and obese women: the role of posture allocation. *Obesity (Silver Spring)*. Jan 2008;16(1):34-9.
993 doi:10.1038/oby.2007.15
- 994 73. Jakicic JM, Powell KE, Campbell WW, et al. Physical Activity and the Prevention of Weight
995 Gain in Adults: A Systematic Review. *Med Sci Sports Exerc*. Jun 2019;51(6):1262-1269.
996 doi:10.1249/MSS.0000000000001938
- 997 74. Catenacci VA, Grunwald GK, Ingebrigtsen JP, et al. Physical activity patterns using
998 accelerometry in the National Weight Control Registry. *Obesity (Silver Spring)*. Jun 2011;19(6):1163-
999 70. doi:10.1038/oby.2010.264
- 1000 75. Catenacci VA, Odgen L, Phelan S, et al. Dietary habits and weight maintenance success in high
1001 versus low exercisers in the National Weight Control Registry. *J Phys Act Health*. Nov 2014;11(8):1540-
1002 8. doi:10.1123/jpah.2012-0250

- 1003 76. Catenacci VA, Ogden LG, Stuht J, et al. Physical activity patterns in the National Weight
1004 Control Registry. *Obesity (Silver Spring)*. Jan 2008;16(1):153-61. doi:10.1038/oby.2007.6
- 1005 77. McGuire MT, Wing RR, Klem ML, Seagle HM, Hill JO. Long-term maintenance of weight
1006 loss: do people who lose weight through various weight loss methods use different behaviors to maintain
1007 their weight? *Int J Obes Relat Metab Disord*. Jun 1998;22(6):572-7. doi:10.1038/sj.ijo.0800627
- 1008 78. Barone Gibbs B, Pettee Gabriel K, Carnethon MR, et al. Sedentary Time, Physical Activity, and
1009 Adiposity: Cross-sectional and Longitudinal Associations in CARDIA. *Am J Prev Med*. Dec
1010 2017;53(6):764-771. doi:10.1016/j.amepre.2017.07.009
- 1011 79. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary
1012 behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA*. Apr 9
1013 2003;289(14):1785-91. doi:10.1001/jama.289.14.1785
- 1014 80. Campbell SDI, Brosnan BJ, Chu AKY, et al. Sedentary Behavior and Body Weight and
1015 Composition in Adults: A Systematic Review and Meta-analysis of Prospective Studies. *Sports Med*.
1016 Mar 2018;48(3):585-595. doi:10.1007/s40279-017-0828-6
- 1017 81. Celis-Morales CA, Perez-Bravo F, Ibanez L, Salas C, Bailey ME, Gill JM. Objective vs. self-
1018 reported physical activity and sedentary time: effects of measurement method on relationships with risk
1019 biomarkers. *PLoS One*. 2012;7(5):e36345. doi:10.1371/journal.pone.0036345
- 1020 82. Creasy SA, Rynders CA, Bergouignan A, Kealey EH, Bessesen DH. Free-Living Responses in
1021 Energy Balance to Short-Term Overfeeding in Adults Differing in Propensity for Obesity. *Obesity*
1022 *(Silver Spring)*. Apr 2018;26(4):696-702. doi:10.1002/oby.22121
- 1023 83. Simon C, Wagner A, Platat C, et al. ICAPS: a multilevel program to improve physical activity
1024 in adolescents. *Diabetes Metab*. Feb 2006;32(1):41-9. doi:10.1016/s1262-3636(07)70245-8
- 1025 84. Simon C, Kellou N, Dugas J, et al. A socio-ecological approach promoting physical activity and
1026 limiting sedentary behavior in adolescence showed weight benefits maintained 2.5 years after
1027 intervention cessation. *Int J Obes (Lond)*. Jul 2014;38(7):936-43. doi:10.1038/ijo.2014.23
- 1028 85. Ezendam NP, Oenema A, van de Looij-Jansen PM, Brug J. Design and evaluation protocol of
1029 "FATaintPHAT", a computer-tailored intervention to prevent excessive weight gain in adolescents.
1030 *BMC Public Health*. Nov 12 2007;7:324. doi:10.1186/1471-2458-7-324
- 1031 86. Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS. The role of exercise and physical
1032 activity in weight loss and maintenance. *Prog Cardiovasc Dis*. Jan-Feb 2014;56(4):441-7.
1033 doi:10.1016/j.pcad.2013.09.012
- 1034 87. Swift DL, McGee JE, Earnest CP, Carlisle E, Nygard M, Johannsen NM. The Effects of
1035 Exercise and Physical Activity on Weight Loss and Maintenance. *Prog Cardiovasc Dis*. Jul - Aug
1036 2018;61(2):206-213. doi:10.1016/j.pcad.2018.07.014
- 1037 88. Donnelly JE, Hill JO, Jacobsen DJ, et al. Effects of a 16-month randomized controlled exercise
1038 trial on body weight and composition in young, overweight men and women: the Midwest Exercise
1039 Trial. *Arch Intern Med*. Jun 9 2003;163(11):1343-50. doi:10.1001/archinte.163.11.1343
- 1040 89. Donnelly JE, Honas JJ, Smith BK, et al. Aerobic exercise alone results in clinically significant
1041 weight loss for men and women: midwest exercise trial 2. *Obesity (Silver Spring)*. Mar
1042 2013;21(3):E219-28. doi:10.1002/oby.20145
- 1043 90. Herrmann SD, Willis EA, Honas JJ, Lee J, Washburn RA, Donnelly JE. Energy intake,
1044 nonexercise physical activity, and weight loss in responders and nonresponders: The Midwest Exercise
1045 Trial 2. *Obesity (Silver Spring)*. Aug 2015;23(8):1539-49. doi:10.1002/oby.21073
- 1046 91. Höchsmann C, Dorling JL, Apolzan JW, Johannsen NM, Hsia DS, Martin CK. Baseline
1047 Habitual Physical Activity Predicts Weight Loss, Weight Compensation, and Energy Intake During
1048 Aerobic Exercise. *Obesity (Silver Spring)*. May 2020;28(5):882-892. doi:10.1002/oby.22766
- 1049 92. Jakicic JM, Tate DF, Lang W, et al. Objective physical activity and weight loss in adults: the
1050 step-up randomized clinical trial. *Obesity (Silver Spring)*. Nov 2014;22(11):2284-92.
1051 doi:10.1002/oby.20830
- 1052 93. Kerrigan SG, Call C, Schaumberg K, Forman E, Butryn ML. Associations between change in
1053 sedentary behavior and outcome in standard behavioral weight loss treatment. *Transl Behav Med*. Mar
1054 1 2018;8(2):299-304. doi:10.1093/tbm/ibx038

- 1055 94. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on
1056 hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. Nov 24
1057 2010;304(20):2253-62. doi:10.1001/jama.2010.1710
- 1058 95. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on
1059 cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated
1060 blood pressure: a randomized controlled trial. *JAMA*. May 16 2007;297(19):2081-91.
1061 doi:10.1001/jama.297.19.2081
- 1062 96. Slentz CA, Duscha BD, Johnson JL, et al. Effects of the amount of exercise on body weight,
1063 body composition, and measures of central obesity: STRRIDE--a randomized controlled study. *Arch*
1064 *Intern Med*. Jan 12 2004;164(1):31-9. doi:10.1001/archinte.164.1.31
- 1065 97. Donnelly JE, Blair SN, Jakicic JM, et al. American College of Sports Medicine Position Stand.
1066 Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for
1067 adults. *Med Sci Sports Exerc*. Feb 2009;41(2):459-71. doi:10.1249/MSS.0b013e3181949333
- 1068 98. Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA. Resistance to exercise-induced
1069 weight loss: compensatory behavioral adaptations. *Med Sci Sports Exerc*. Aug 2013;45(8):1600-9.
1070 doi:10.1249/MSS.0b013e31828ba942
- 1071 99. Riou ME, Jomphe-Tremblay S, Lamothe G, et al. Energy Compensation Following a Supervised
1072 Exercise Intervention in Women Living With Overweight/Obesity Is Accompanied by an Early and
1073 Sustained Decrease in Non-structured Physical Activity. *Front Physiol*. 2019 2019;10:1048.
1074 doi:10.3389/fphys.2019.01048
- 1075 100. Lefai E, Blanc S, Momken I, et al. Exercise training improves fat metabolism independent of
1076 total energy expenditure in sedentary overweight men, but does not restore lean metabolic phenotype.
1077 *Int J Obes (Lond)*. Dec 2017;41(12):1728-1736. doi:10.1038/ijo.2017.151
- 1078 101. Villablanca PA, Alegria JR, Mookadam F, Holmes DR, Jr., Wright RS, Levine JA. Nonexercise
1079 activity thermogenesis in obesity management. *Mayo Clin Proc*. Apr 2015;90(4):509-19.
1080 doi:10.1016/j.mayocp.2015.02.001
- 1081 102. Levine JA. Non-exercise activity thermogenesis. *Proc Nutr Soc*. Aug 2003;62(3):667-79.
1082 doi:10.1079/PNS2003281
- 1083 103. Swift DL, Nevels TR, Solar CA, et al. The Effect of Aerobic Training and Increasing
1084 Nonexercise Physical Activity on Cardiometabolic Risk Factors. *Med Sci Sports Exerc*. Oct 1
1085 2021;53(10):2152-2163. doi:10.1249/MSS.0000000000002675
- 1086 104. Hadgraft NT, Winkler E, Climie RE, et al. Effects of sedentary behaviour interventions on
1087 biomarkers of cardiometabolic risk in adults: systematic review with meta-analyses. *Br J Sports Med*.
1088 Feb 2021;55(3):144-154. doi:10.1136/bjsports-2019-101154
- 1089 105. Nieste I, Franssen WMA, Spaas J, Bruckers L, Savelberg H, Eijnde BO. Lifestyle interventions
1090 to reduce sedentary behaviour in clinical populations: A systematic review and meta-analysis of
1091 different strategies and effects on cardiometabolic health. *Prev Med*. Jul 2021;148:106593.
1092 doi:10.1016/j.ypmed.2021.106593
- 1093 106. Fanning J, Rejeski WJ, Leng I, et al. Intervening on exercise and daylong movement for weight
1094 loss maintenance in older adults: A randomized, clinical trial. *Obesity (Silver Spring)*. Jan
1095 2022;30(1):85-95. doi:10.1002/oby.23318
- 1096 107. Saeidifard F, Medina-Inojosa JR, Supervia M, et al. The Effect of Replacing Sitting With
1097 Standing on Cardiovascular Risk Factors: A Systematic Review and Meta-analysis. *Mayo Clin Proc*
1098 *Innov Qual Outcomes*. Dec 2020;4(6):611-626. doi:10.1016/j.mayocpiqo.2020.07.017
- 1099 108. Borg P, Kukkonen-Harjula K, Fogelholm M, Pasanen M. Effects of walking or resistance
1100 training on weight loss maintenance in obese, middle-aged men: a randomized trial. *Int J Obes Relat*
1101 *Metab Disord*. May 2002;26(5):676-83. doi:10.1038/sj.ijo.0801962
- 1102 109. Fogelholm M, Kukkonen-Harjula K, Nenonen A, Pasanen M. Effects of walking training on
1103 weight maintenance after a very-low-energy diet in premenopausal obese women: a randomized
1104 controlled trial. *Arch Intern Med*. Jul 24 2000;160(14):2177-84.
- 1105 110. Jakicic JM, Marcus BH, Lang W, Janney C. Effect of exercise on 24-month weight loss
1106 maintenance in overweight women. *Arch Intern Med*. Jul 28 2008;168(14):1550-9; discussion 1559-60.
1107 doi:10.1001/archinte.168.14.1550

- 1108 111. Jeffery RW, Wing RR, Sherwood NE, Tate DF. Physical activity and weight loss: does
1109 prescribing higher physical activity goals improve outcome? *Am J Clin Nutr.* Oct 2003;78(4):684-9.
- 1110 112. Leermakers EA, Perri MG, Shigaki CL, Fuller PR. Effects of exercise-focused versus weight-
1111 focused maintenance programs on the management of obesity. *Addict Behav.* Mar-Apr 1999;24(2):219-
1112 27.
- 1113 113. Pavlou KN, Krey S, Steffee WP. Exercise as an adjunct to weight loss and maintenance in
1114 moderately obese subjects. *Am J Clin Nutr.* May 1989;49(5 Suppl):1115-23.
- 1115 114. Perri MG, McAdoo WG, McAllister DA, Lauer JB, Yancey DZ. Enhancing the efficacy of
1116 behavior therapy for obesity: effects of aerobic exercise and a multicomponent maintenance program. *J*
1117 *Consult Clin Psychol.* Oct 1986;54(5):670-5.
- 1118 115. Skender ML, Goodrick GK, Del Junco DJ, et al. Comparison of 2-year weight loss trends in
1119 behavioral treatments of obesity: diet, exercise, and combination interventions. *J Am Diet Assoc.* Apr
1120 1996;96(4):342-6. doi:10.1016/S0002-8223(96)00096-X
- 1121 116. Tate DF, Jeffery RW, Sherwood NE, Wing RR. Long-term weight losses associated with
1122 prescription of higher physical activity goals. Are higher levels of physical activity protective against
1123 weight regain? *Am J Clin Nutr.* Apr 2007;85(4):954-9.
- 1124 117. Wing RR, Venditti E, Jakicic JM, Polley BA, Lang W. Lifestyle intervention in overweight
1125 individuals with a family history of diabetes. *Diabetes Care.* Mar 1998;21(3):350-9.
- 1126 118. King NA, Caudwell P, Hopkins M, et al. Metabolic and behavioral compensatory responses to
1127 exercise interventions: barriers to weight loss. *Obesity (Silver Spring).* Jun 2007;15(6):1373-83.
1128 doi:10.1038/oby.2007.164
- 1129 119. Pontzer H, Durazo-Arvizu R, Dugas LR, et al. Constrained Total Energy Expenditure and
1130 Metabolic Adaptation to Physical Activity in Adult Humans. *Curr Biol.* Feb 8 2016;26(3):410-7.
1131 doi:10.1016/j.cub.2015.12.046
- 1132 120. Hunter GR, Fisher G, Neumeier WH, Carter SJ, Plaisance EP. Exercise Training and Energy
1133 Expenditure following Weight Loss. *Med Sci Sports Exerc.* Sep 2015;47(9):1950-7.
1134 doi:10.1249/MSS.0000000000000622
- 1135 121. Wang X, Bowyer KP, Porter RR, Breneman CB, Custer SS. Energy expenditure responses to
1136 exercise training in older women. *Physiol Rep.* Aug 2017;5(15):e13360. doi:10.14814/phy2.13360
- 1137 122. Goran MI, Poehlman ET. Endurance training does not enhance total energy expenditure in
1138 healthy elderly persons. *Am J Physiol.* Nov 1992;263(5 Pt 1):E950-7.
1139 doi:10.1152/ajpendo.1992.263.5.E950
- 1140 123. Whybrow S, Hughes DA, Ritz P, et al. The effect of an incremental increase in exercise on
1141 appetite, eating behaviour and energy balance in lean men and women feeding ad libitum. *Br J Nutr.*
1142 Nov 2008;100(5):1109-15. doi:10.1017/S0007114508968240
- 1143 124. Careau V, Halsey LG, Pontzer H, et al. Energy compensation and adiposity in humans. *Curr*
1144 *Biol.* Oct 25 2021;31(20):4659-4666 e2. doi:10.1016/j.cub.2021.08.016
- 1145 125. Willis EA, Creasy SA, Saint-Maurice PF, et al. Physical Activity and Total Daily Energy
1146 Expenditure in Older US Adults: Constrained versus Additive Models. *Med Sci Sports Exerc.* Jul 30
1147 2021;doi:10.1249/MSS.0000000000002759
- 1148 126. Flack KD, Hays HM, Moreland J, Long DE. Exercise for Weight Loss: Further Evaluating
1149 Energy Compensation with Exercise. *Med Sci Sports Exerc.* Nov 2020;52(11):2466-2475.
1150 doi:10.1249/MSS.0000000000002376
- 1151 127. Speakman JR. Thrifty genes for obesity, an attractive but flawed idea, and an alternative
1152 perspective: the 'drifty gene' hypothesis. *Int J Obes (Lond).* Nov 2008;32(11):1611-7.
1153 doi:10.1038/ijo.2008.161
- 1154 128. Ostendorf DM, Caldwell AE, Creasy SA, et al. Physical Activity Energy Expenditure and Total
1155 Daily Energy Expenditure in Successful Weight Loss Maintainers. *Obesity (Silver Spring).* Mar
1156 2019;27(3):496-504. doi:10.1002/oby.22373
- 1157 129. Ostendorf DM, Lyden K, Pan Z, et al. Objectively Measured Physical Activity and Sedentary
1158 Behavior in Successful Weight Loss Maintainers. *Obesity (Silver Spring).* Jan 2018;26(1):53-60.
1159 doi:10.1002/oby.22052

- 1160 130. Mayer J, Roy P, Mitra KP. Relation between caloric intake, body weight, and physical work:
1161 studies in an industrial male population in West Bengal. *Am J Clin Nutr.* Mar-Apr 1956;4(2):169-75.
1162 doi:10.1093/ajcn/4.2.169
- 1163 131. Beaulieu K, Hopkins M, Blundell J, Finlayson G. Homeostatic and non-homeostatic appetite
1164 control along the spectrum of physical activity levels: An updated perspective. *Physiol Behav.* Aug 1
1165 2018;192:23-29. doi:10.1016/j.physbeh.2017.12.032
- 1166 132. Berthoud HR. Metabolic and hedonic drives in the neural control of appetite: who is the boss?
1167 *Curr Opin Neurobiol.* Dec 2011;21(6):888-96. doi:10.1016/j.conb.2011.09.004
- 1168 133. Shook RP, Hand GA, Drenowatz C, et al. Low levels of physical activity are associated with
1169 dysregulation of energy intake and fat mass gain over 1 year. *Am J Clin Nutr.* Dec 2015;102(6):1332-8.
1170 doi:10.3945/ajcn.115.115360
- 1171 134. Stubbs RJ, Hughes DA, Johnstone AM, Horgan GW, King N, Blundell JE. A decrease in
1172 physical activity affects appetite, energy, and nutrient balance in lean men feeding ad libitum. *Am J Clin*
1173 *Nutr.* Jan 2004;79(1):62-9. doi:10.1093/ajcn/79.1.62
- 1174 135. Chaput JP, Drapeau V, Poirier P, Teasdale N, Tremblay A. Glycemic instability and
1175 spontaneous energy intake: association with knowledge-based work. *Psychosom Med.* Sep
1176 2008;70(7):797-804. doi:10.1097/PSY.0b013e31818426fa
- 1177 136. Pearson N, Biddle SJ. Sedentary behavior and dietary intake in children, adolescents, and adults.
1178 A systematic review. *Am J Prev Med.* Aug 2011;41(2):178-88. doi:10.1016/j.amepre.2011.05.002
- 1179 137. Hobbs M, Pearson N, Foster PJ, Biddle SJ. Sedentary behaviour and diet across the lifespan: an
1180 updated systematic review. *Br J Sports Med.* Sep 2015;49(18):1179-88. doi:10.1136/bjsports-2014-
1181 093754
- 1182 138. Chaput JP, Visby T, Nyby S, et al. Video game playing increases food intake in adolescents: a
1183 randomized crossover study. *Am J Clin Nutr.* Jun 2011;93(6):1196-203. doi:10.3945/ajcn.110.008680
- 1184 139. Prentice A, Jebb S. Energy intake/physical activity interactions in the homeostasis of body
1185 weight regulation. *Nutr Rev.* Jul 2004;62(7 Pt 2):S98-104. doi:10.1111/j.1753-4887.2004.tb00095.x
- 1186 140. Myers A, Gibbons C, Finlayson G, Blundell J. Associations among sedentary and active
1187 behaviours, body fat and appetite dysregulation: investigating the myth of physical inactivity and
1188 obesity. *Br J Sports Med.* Nov 2017;51(21):1540-1544. doi:10.1136/bjsports-2015-095640
- 1189 141. Bergouignan A, Legget KT, De Jong N, et al. Effect of frequent interruptions of prolonged
1190 sitting on self-perceived levels of energy, mood, food cravings and cognitive function. *Int J Behav Nutr*
1191 *Phys Act.* Nov 3 2016;13(1):113. doi:10.1186/s12966-016-0437-z
- 1192 142. Maclean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the
1193 impetus for weight regain. *Am J Physiol Regul Integr Comp Physiol.* Sep 2011;301(3):R581-600.
1194 doi:10.1152/ajpregu.00755.2010
- 1195 143. Dulloo AG, Jacquet J, Miles-Chan JL, Schutz Y. Passive and active roles of fat-free mass in the
1196 control of energy intake and body composition regulation. *Eur J Clin Nutr.* Mar 2017;71(3):353-357.
1197 doi:10.1038/ejcn.2016.256
- 1198 144. Blundell JE, Gibbons C, Beaulieu K, et al. The drive to eat in homo sapiens: Energy expenditure
1199 drives energy intake. *Physiol Behav.* May 15 2020;219:112846. doi:10.1016/j.physbeh.2020.112846
- 1200 145. Hollstein T, Heinitz S, Basolo A, Krakoff J, Votruba SB, Piaggi P. Reduced metabolic efficiency
1201 in sedentary eucaloric conditions predicts greater weight regain in adults with obesity following
1202 sustained weight loss. *Int J Obes (Lond).* Apr 2021;45(4):840-849. doi:10.1038/s41366-021-00748-y
- 1203 146. Stensel DJ, King JA, Thackray AE. Role of physical activity in regulating appetite and body fat.
1204 *Nutrition Bulletin.* 2016 2016;41(4):314-322. doi:10.1111/nbu.12234
- 1205 147. Martins C, Truby H, Morgan LM. Short-term appetite control in response to a 6-week exercise
1206 programme in sedentary volunteers. *Br J Nutr.* Oct 2007;98(4):834-42.
1207 doi:10.1017/S000711450774922X
- 1208 148. King NA, Caudwell PP, Hopkins M, Stubbs JR, Naslund E, Blundell JE. Dual-process action of
1209 exercise on appetite control: increase in orexigenic drive but improvement in meal-induced satiety. *Am*
1210 *J Clin Nutr.* Oct 2009;90(4):921-7. doi:10.3945/ajcn.2009.27706

- 1211 149. Bergouignan A, Momken I, Schoeller DA, et al. Regulation of energy balance during long-term
1212 physical inactivity induced by bed rest with and without exercise training. *J Clin Endocrinol Metab.*
1213 Mar 2010;95(3):1045-53. doi:10.1210/jc.2009-1005
- 1214 150. Ravussin E, Schutz Y, Acheson KJ, Dusmet M, Bourquin L, Jequier E. Short-term, mixed-diet
1215 overfeeding in man: no evidence for "luxuskonsumption". *Am J Physiol.* Nov 1985;249(5 Pt 1):E470-7.
1216 doi:10.1152/ajpendo.1985.249.5.E470
- 1217 151. Johannsen DL, Marlatt KL, Conley KE, Smith SR, Ravussin E. Metabolic adaptation is not
1218 observed after 8 weeks of overfeeding but energy expenditure variability is associated with weight
1219 recovery. *Am J Clin Nutr.* Oct 1 2019;110(4):805-813. doi:10.1093/ajcn/nqz108
- 1220 152. Bray GA, Bouchard C. The biology of human overfeeding: A systematic review. *Obes Rev.* Sep
1221 2020;21(9):e13040. doi:10.1111/obr.13040
- 1222 153. Flatt JP. Carbohydrate-fat interactions and obesity examined by a two-compartment computer
1223 model. *Obes Res.* Dec 2004;12(12):2013-22. doi:10.1038/oby.2004.252
- 1224 154. Schrauwen P, Lichtenbelt WD, Saris WH, Westerterp KR. Fat balance in obese subjects: role
1225 of glycogen stores. *Am J Physiol.* Jun 1998;274(6):E1027-33. doi:10.1152/ajpendo.1998.274.6.E1027
- 1226 155. Bergouignan A, Rudwill F, Simon C, Blanc S. Physical inactivity as the culprit of metabolic
1227 inflexibility: evidence from bed-rest studies. *J Appl Physiol (1985).* Oct 2011;111(4):1201-10.
1228 doi:10.1152/jappphysiol.00698.2011
- 1229 156. Kelley DE, Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a
1230 reexamination. *Diabetes.* May 2000;49(5):677-83. doi:10.2337/diabetes.49.5.677
- 1231 157. Galgani JE, Fernandez-Verdejo R. Pathophysiological role of metabolic flexibility on metabolic
1232 health. *Obes Rev.* Feb 2021;22(2):e13131. doi:10.1111/obr.13131
- 1233 158. Bergouignan A, Momken I, Lefai E, et al. Activity energy expenditure is a major determinant
1234 of dietary fat oxidation and trafficking, but the deleterious effect of detraining is more marked than the
1235 beneficial effect of training at current recommendations. *Am J Clin Nutr.* Sep 2013;98(3):648-58.
1236 doi:10.3945/ajcn.112.057075
- 1237 159. Bergouignan A, Rudwill F, Simon C, Blanc S. Physical inactivity as the culprit of metabolic
1238 inflexibility: evidence from bed-rest studies. *Journal of Applied Physiology.* OCT 2011
1239 2011;111(4):1201-1210. doi:10.1152/jappphysiol.00698.2011
- 1240 160. Bergouignan A, Antoun E, Momken I, et al. Effect of contrasted levels of habitual physical
1241 activity on metabolic flexibility. *J Appl Physiol (1985).* Feb 2013;114(3):371-9.
1242 doi:10.1152/jappphysiol.00458.2012
- 1243 161. Rynders CA, Blanc S, DeJong N, Bessesen DH, Bergouignan A. Sedentary behaviour is a key
1244 determinant of metabolic inflexibility. *J Physiol.* Apr 15 2018;596(8):1319-1330.
1245 doi:10.1113/JP273282
- 1246 162. Rynders C, Pereira R, Bergouignan A, Kealey E, Bessesen D. Associations among dietary fat
1247 oxidation responses to overfeeding and weight gain in obesity-prone and resistant adults.: *Obesity*; 2018.
- 1248 163. Egger G, Swinburn B. An "ecological" approach to the obesity pandemic. *BMJ.* Aug 23
1249 1997;315(7106):477-80. doi:10.1136/bmj.315.7106.477
- 1250 164. Owen N, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: emerging
1251 evidence for a new health risk. *Mayo Clin Proc.* Dec 2010;85(12):1138-41. doi:10.4065/mcp.2010.0444
- 1252 165. Wang Z, Deurenberg P, Heymsfield SB. Cellular-level body composition model. A new
1253 approach to studying fat-free mass hydration. *Ann N Y Acad Sci.* May 2000;904:306-11.
1254 doi:10.1111/j.1749-6632.2000.tb06472.x

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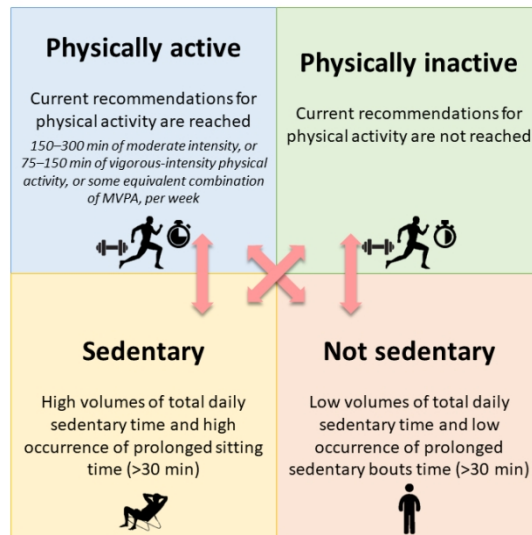


Figure 1: Schematic representation of the four observable behaviors across the spectrum of physical activity and sedentary behavior. Of note, no specific recommendations currently exist for being or not being sedentary. Abbreviation: MVPA: moderate-to-vigorous physical activity

338x190mm (96 x 96 DPI)

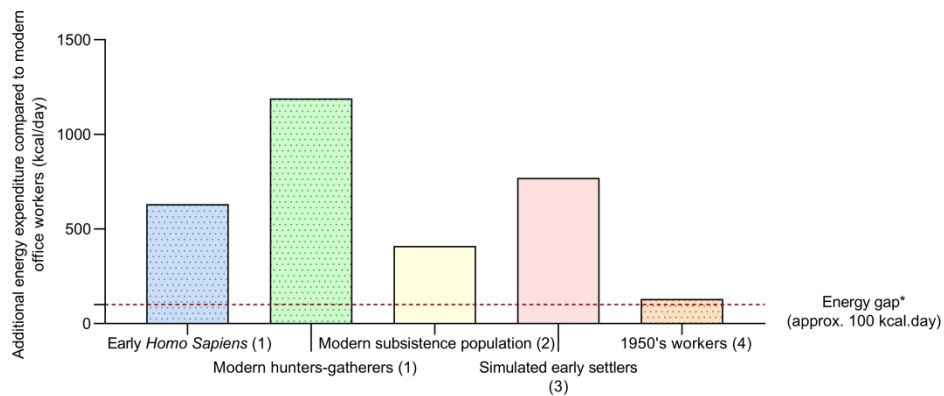


Figure 2: Schematic representation of the extra energy expended by early *Homo sapiens*, modern hunter-gatherers, modern subsistence populations, and workers of the 1950's compared to the total daily energy expenditure of modern office workers. Spotted bars represent estimated data, and plain bars represent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

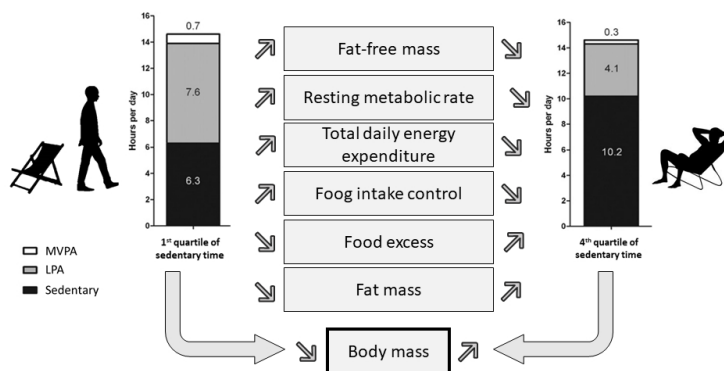


Figure 3: Schematic representation of the effects of sedentary behaviors on the components of energy balance and hence, body weight regulation. Using the data of Owen et al.¹⁶⁴, the left side of the figure represents a non-sedentary person (10th percentile of total daily sedentary time) while the right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

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