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REVIEW

Sick of sitting

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Abstract Sitting too much kills. Epidemiological, physiological and molecular data suggest that sedentary lifestyle can explain, in part, how modernity is associated with obesity, more than 30 chronic diseases and conditions and high healthcare costs. Excessive sitting—sitting disease—is not innate to the human condition. People were designed to be bipedal and, before the industrial revolution, people moved substantially more throughout the day than they do presently. It is encouraging that solutions exist to reverse sitting disease. Work environments, schools, communities and cities can be re-imagined and re-invented as walking spaces, and people thereby offered more active, happier, healthier and more productive lives.

Keywords Chronic disease · Diabetes · Non-exercise activity thermogenesis · Obesity · Physical activity · Review

Abbreviations
NEAT Non-exercise activity thermogenesis

In the beginning, we were bipedal

There is debate regarding the evolutionary steps that resulted in bipedalism [1]; suffice it to say, the human evolved over hundreds of thousands of years to be upright, two-legged, walking beings [2–6]. Over time, people evolved to explore by foot, to manually invent tools and weapons and to think while upright and responding to environmental cues, perceived threats and calculated opportunities [7]. Thousands of years ago, living was dynamic. Compare chasing a bison over a cliff to choosing a meat package at the supermarket and contrast hand-chipping a flint for a spear versus engineering a cyber attack. Prior to the industrial revolution 200 years ago, 90% of the world's population lived in agricultural communities where shelter, nutrition and reproduction all required physical exertion. Data from agricultural communities suggest that, prior to the industrial revolution, people sat for 300 min per day and lived actively [8]. From 1760 onward, the industrial revolution precipitated urbanisation; it was the predominant demographic shift into modern history [9–11]. Now more than half the world's population live in cities and urbanisation continues to grow worldwide [12]. In industrialising countries, 1908 saw the introduction of factories that used conveyor belts, and in the 1940s, modern chair-based offices were developed. In both cases, the environments and furnishings were designed to promote productivity and limit movement by having people sit. Walking around factories or offices was perceived as wasted time. Fast-forward to the present day, and office workers can sit for up to 15 h in a single day! [13].

People are designed to work and socialise while on their legs and to sit in order to rest; the default position for people is to be up and moving. Is it a surprise that modern people who default to sitting (e.g. 'take a seat') experience negative physical, medical and psychological consequences? Do modern environments, however, give us any other choice except to sit?

Modern environments foster sitting

Environments foster sedentariness in many ways and at multiple societal levels. On an individual level, a person is confronted with environmental cues to sit throughout the day, e.g. drive-through banks [14]. Modern homes contain many tools of convenience, each one decreasing non-

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exercise activity thermogenesis (NEAT) [15]. Workplaces [16, 17] and schools [18–20] are major environmental drivers of NEAT. Communities encourage inhabitants to be sedentary. For instance, when data for 3,139 US counties were reviewed, encompassing the majority of the US population, sedentariness correlated with poverty, as did obesity and diabetes [21]. No personal choices, behaviour or genetics can explain this association because people do not choose to live in poverty. Other factors that may explain why people living in poverty-dense areas are likely to be sedentary include crime, poor housing conditions, poor health and lack of access to activity-promoting opportunities.

Cityscapes and sitting

More than half the world's population live in cities, with the fastest growth occurring in some of the world's poorest countries [22]. Active leg-based transportation is common in a number of European cities, including Copenhagen and Amsterdam. Rain or shine, Amsterdam is swamped with bicycles [23]. In the USA, there is variability in how cityscapes encourage or inhibit walking. New York City, San Francisco, Boston, Philadelphia and Miami are among the most walkable [24, 25], suggesting that weather is not a key determinant. Los Angeles, on the other hand, exemplifies a city that inhibits walking because of poor air quality and a roadway design that imposes the use of motor transport [26, 27]. Los Angeles has the most congested streets in the USA. The average Los Angeles driver experiences 72 h of traffic delays per year. Overall, US drivers waste 3 billion gallons of gas per year and 6 billion hours sitting in traffic [28]. Cityscapes that promote sedentariness are unhealthy in other ways, too.

Public policy [29] and prevailing social ambience can impact sitting [30–32]. In many societies, gender- and age-defined roles impact sedentariness [32–34]. Stereotypes about obesity can perpetuate low NEAT, promote bullying in children and permit discrimination [35–38]. Religion, too, can factor into promoting sedentariness [39].

Overall, the environment influences sitting in multiple ways. The precise magnitude of environmental influences on NEAT and/or sitting is poorly quantified because it is difficult to conduct societal-wide sedentariness research, gather valid population data and account appropriately for the vast array of variables as wide-ranging as religion, sociology, wealth and weather.

The impact of sitting on the human body. The physiology of sitting too much

Studies illustrate the physiological implications of sedentariness. Sixteen lean, healthy volunteers were overfed 1,000 kcal/day (4.18 MJ/day) above their weight maintenance needs for 2 months. Those volunteers who increased their NEAT the most gained the least amount of body fat. Some volunteers increased their NEAT by >700 kcal/day (>2.93 MJ/day) [40, 41]. Conversely, those people who did not increase their NEAT—those who stayed seated—were the most prone to gain body fat.

Underwear interlaced with sensors that captured body postures and movement was used to examine how a person can increase their NEAT by >700 kcal/day (>2.93 MJ/day). People who increase habitual walking (not purposeful exercise) can 'burn-off' the excesses of consumption. Conversely, people who overeat and stay seated gain the most body fat [41].

Human energetics can explain how NEAT can vary so greatly depending on how a person lives. Basal energy expenditure is the energy a person expends at complete rest. It increases with greater body size [42]. A seated person working at a computer screen generally expends 5% above basal energy expenditure—10–20 kcal/h (0.04–0.08 MJ/h) [42]. Within minutes of standing and walking, a person's energy expenditure doubles. An average person moving at 1–2 mph (1.6–3.2 kph) expends 100–250 kcal/h (0.42–1 MJ/h) above basal energy expenditure [42]. The standard workday of three hypothetical office workers are compared in Fig. 1. The figure illustrates that, during work hours alone, one worker can expend 1,000 kcal/day (4.2 MJ/day) more than another worker, even when both people have similar desk-based jobs. This accounting does not even consider the energy expenditure of leisure, which also varies greatly from sedentary screen time (100 kcal/evening) (0.42 MJ/evening) to active leisure (500–1,000 kcal/evening) (2.1–4.2 MJ/evening). It is not surprising, therefore, that when a group of people with similar desk-based jobs is studied, those who sit more have greater body fat than those who walk more [43, 44]. Interestingly, people who are most active in their leisure time are also most active at work [43]. Overall, people with obesity tend to sit for 2.5 h per day more than lean people with similar professions, economic statuses and home environments [44]. People with obesity tend to sit; walkers tend to be leaner.

There are other physiological factors that influence NEAT, including age, weather, concomitant illness, medications and sleep [45–48]. Sleep deprivation, for example, is associated with obesity [49–51] because, when people are deprived of sleep, their cumulative daily NEAT does not increase, despite their being awake for longer. Energy intake, however, does increase [52]. In sleep deprivation, positive energy balance and weight gain occur through the disassociation of energy intake from NEAT. It is interesting that a key neurochemical involved in wakefulness, orexin, is also a direct mediator of NEAT [53–55] and is integrated into the feeding circuits [56].

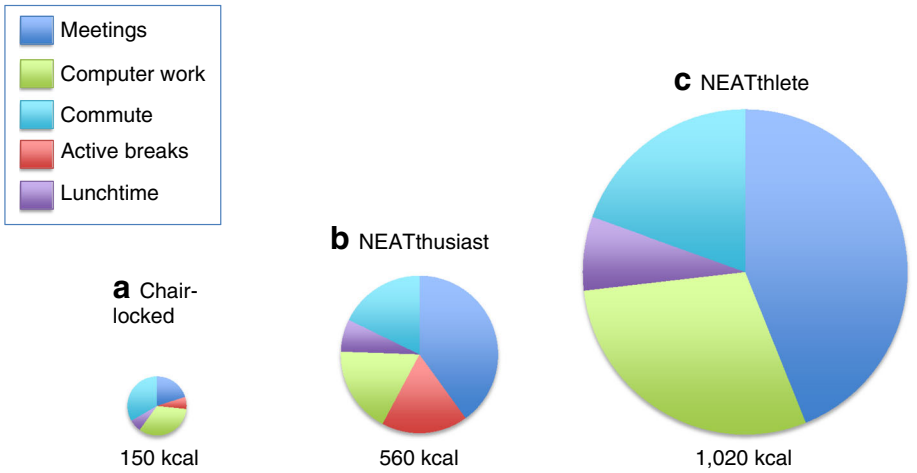

Fig. 1 Hypothetical workplace energy expenditures for (**a**) The chair-locked worker who sits most of the day; (**b**) the NEATthusiast who converts half of their six, 0.5-h meetings to walking meetings, parks a little farther away from the office, and takes 10 min 'active breaks' during the work day and a brief stroll at lunch time; and (**c**) the NEATthlete who conducts all work meetings while walking, has a chair-less desk, takes a 0.5 h walk at lunchtime and cycles to work

The molecular biology of sitting too much

Minor, short bursts of NEAT break up sitting and activate multiple molecular mechanisms. For example, in muscle, NEAT bursts improve insulin handling [57] via mitochondrial factors, lipolysis and insulin-receptor action [58–62]. The aforementioned associations between sitting, adiposity, insulin sensitivity and metabolic dysfunction can explain the association between excess sitting and cancer, in part [63–65]. Excess sitting also disrupts sex hormone function, insulin-like growth factors, inflammation and vitamin handling [66]. Prolonged sitting adversely impacts bone growth factors [67, 68] and, coupled with decreased weight bearing, sitting is associated with lower bone mineral density and osteoporosis [69, 70]. Being seated alters the activation patterns of multiple weight-bearing muscles and, therefore, excessive desk use is associated with adverse back curvature, back pain [71–74] and upper extremity problems such as carpel tunnel syndrome [75, 76]. Movement is neurologically linked to brain centres outside the motor control centres [53, 77–85]. Perhaps this assembly can explain the relationship between sedentariness, low mood, depression and dulled intellectual function [86, 87]. Furthermore, a person's predisposition to sitting is partially predicated by genetic factors, although how these factors interface with environmental cues is not understood [14, 88–90].

En masse, the physiological evidence suggests that high levels of NEAT occur in the lean population, whereas low NEAT/sedentariness is linked to obesity. Sitting is ultimately a behaviour with environmental, sociological and biological cues. The organisational hub is in the brain.

The chair-locked brain

When people overeat, NEAT increases. This suggests that circuits exist to integrate food intake and NEAT [91]. For example, if a person rakes leaves all day, they become hungry. It is unlikely that the integration of NEAT and food intake is limited to humans, because when wolves, horses and dogs run a lot, they eat a lot, too [92].

While overeating increases NEAT, starvation decreases NEAT. Keys and colleagues showed that prisoners decreased their spontaneous movements when starved [93, 94]. The link between starvation and NEAT occurs across species and genera [95, 96]. All species that have been studied show similar responses to starvation: first, there is a short-term increase in NEAT (ascribed to foraging), but once starvation is prolonged, NEAT decreases—even in fish [97]. Excess food and undernutrition evoke heightened and lowered NEAT, respectively, implying that a central connection exists between these two variables.

NEAT and energy intake connect in the hypothalamus. Several neuromodulators influence the paraventricular nucleus of the hypothalamus to regulate NEAT, such as orexin A and neuromedin U [54, 56, 80, 98, 99]. Orexin A is especially interesting, as it is an arousal protein associated with wakefulness—the period of the day when people move. When orexin A is injected into the paraventricular nucleus of the hypothalamus, NEAT increases in a dose-dependent fashion. The central effect of orexin A is blunted in rats inbred for obesity [53, 80]. Furthermore, orexin A is directly integrated with neuromodulators of appetite [100], muscle efficiency [53] and adipokines [100, 101]. The complete circuit for these interactions has not been fully mapped. However, these effects, and others like it, could explain why some people with a tendency to develop obesity are predisposed to sitting and eating in excess of energy needs. Conversely, people with heightened responsiveness to NEAT signals move more, have higher NEAT, maintain less body fat and resist obesity.

NEAT is influenced by other sensory inputs. For instance, how does a person who rakes leaves for several hours know that they are tired and sense the need to take a sitting break? What is the hierarchical interplay between behaviour and

neurochemistry whereby a person decides to conduct a professional meeting while walking instead of sitting? In both of these examples, there are likely to be multiple sensory inputs from the musculature, joints, tendons, nerves, metabolic systems and multiple brain regions. The response systems are likely to be hierarchical and complex, whereby NEAT activation is concomitantly affected by behaviour, environment and social cues. Bench-based biology bolsters the evidence that NEAT is regulated principally in the hypothalamus. However, field-based observations suggest that the integration of NEAT with life is complex and functions across the domains of biology, behaviour, environment and sociology; therefore, across many neuroanatomic domains as well.

NEAT changes in response to sudden environmental stimuli, e.g. jumping out of the way of a bus, and with short- and long-term illness, e.g. influenza and congestive heart failure [102]. NEAT also changes over the long term, e.g. with changes in food availability and with the seasons. NEAT changes across a person's lifespan—compare the frenetic energy of a young child [103, 104] to the deliberate gait of an elderly person [45, 105]. The age-decline in NEAT has been linked to changes in telomere length [90]. Historically, most people in agricultural communities moved throughout their day, and now most people sit for most of their day, so it is self-evident that movers can become sitters. If complex neurological systems regulate NEAT, what is the mechanism for NEAT adaptation? The central nervous system—both anatomically and biochemically—contains adaptive mechanisms that enable the brain to change its structure and function. Some of these neuroplasticity factors have been linked to NEAT and, by inference, to sitting [84, 106]. Several human experiments suggest that sitters can become movers [107, 108], and so it is plausible that central neuroplasticity factors influence human NEAT. Perhaps because the brain adapts more rapidly in the young, adaptation to NEAT-promoting environments occurs more readily in the young than in the elderly. Which epigenetic factors are important in NEAT adaptation remain unknown [106].

Excessive sitting occurs in most people in modern society because of sociological, behavioural and biological cues. Excessive sitting is a concern because it is harmful. The illnesses associated with sedentariness are discussed next.

Sitting sickness

Sedentariness and low NEAT may be important factors in obesity [109], but it is less obvious as to why sedentariness is causally associated with diabetes and 33 other chronic diseases and conditions [90]. To illustrate the impact of sitting, in one experiment, healthy volunteers were provided with three meals and encouraged to remain sedentary thereafter. The same participants, on another occasion, were provided with similar meals and asked after they had eaten to walk for 15 min at 1.5 mph (2.4 kph) [110]. Continuous glucose monitoring showed that the short walks halved postprandial glycaemic excursion, regardless of when the meal was consumed. In this instance, and in several other experiments [111, 112], the data underscore how prolonged sitting increases insulin resistance and that breaking up sitting time can improve glucose handling [111–113]. These data provide a physiological rationale as to why sitting is associated with type 2 diabetes and gestational diabetes [114–116].

Thirty-five chronic diseases and conditions are associated with sedentariness [90], including frailty in the elderly [117–120], weight regain after therapeutic weight loss [121, 122], hypertension [123], osteoporosis [69, 124–126], malignancies such as breast [23] and prostate [127] cancer, cardiovascular disease [102, 128], male erectile dysfunction [129], depression [130], and back and musculoskeletal pain [75, 131]. Improved physical activity also helps with addictions to alcohol, opiates and cigarettes [132–135]. Chronic diseases and conditions associated with sedentary behaviour [90] impact approximately 70% of patients [136] and the majority of US healthcare costs [137], and so the fiscal consequences of a sedentary lifestyle are enormous.

Conclusion

Excessive sitting is a common pathway that contributes to numerous chronic diseases such as obesity, type 2 diabetes, cardiovascular disease and multiple types of cancer. Physiological and molecular mechanisms can explain these associations. The good news is that people can adapt; if work places, schools and cityscapes could be designed to promote activity, the new default posture could be up and moving. Upwardly mobile people could become healthier.

Sitting science and solutions to sedentariness are in their infancy. Scientific enquiry is important to understand the causality and consequence of sitting and to validate approaches to reverse sedentariness. But if the curse of lethal sitting is to be reversed, a societal-wide approach is needed.

Sedentariness is a transdisciplinary problem that hurts many people and therefore requires a transdisciplinary response. Entrepreneurs, policy makers, health professionals, teachers, industrialists, lawyers, business leaders, scientists, healthcare providers and other key leaders will need to get up, leave the comfort of their specialties, and achieve change in coalition. Individuals too must stand united. Ultimately, individuals are consumers, control school and company boards, work, attend educational centres, buy stock and decide elections. The challenge of sedentariness is as societal as it is personal: Homo sedentarius, arise.

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