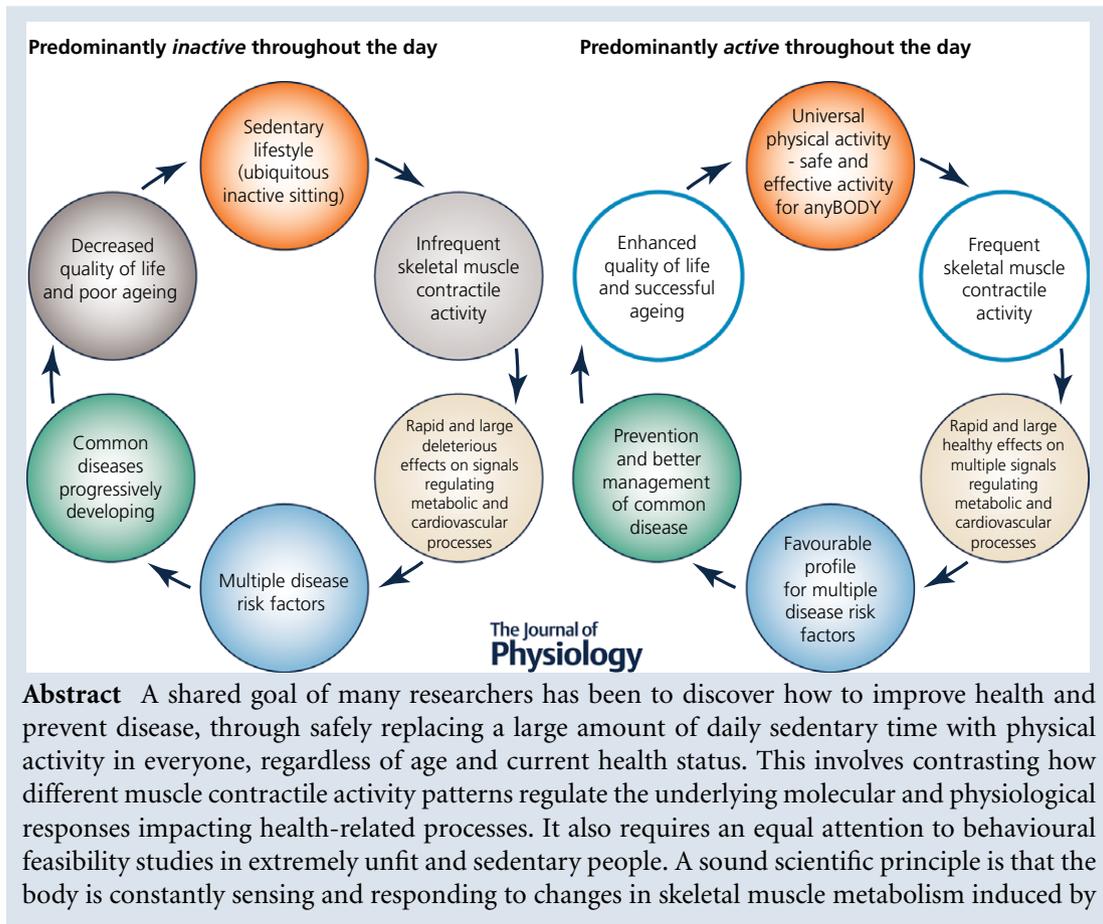


SYMPOSIUM REVIEW

The role of skeletal muscle contractile duration throughout the whole day: reducing sedentary time and promoting universal physical activity in all people

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Marc Hamilton is a Professor who performs research into the physiological processes of how physical inactivity can cause disease (inactivity physiology) and how to optimize healthy effects of skeletal muscle contractile activity in all types of people, but especially in people who are unable to exercise or have pre-existing diseases. He is the Executive Director of a translational research centre recently formed in Houston, TX that will focus on developing a solution for maintaining healthy active lifestyles over the whole lifespan and combatting metabolic and cardiovascular disorders.



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contractile activity. Because of that, the rapid time course of health-related responses to physical inactivity/activity patterns are caused in large part directly because of the variable amounts of muscle inactivity/activity throughout the day. However, traditional modes and doses of exercise fall far short of replacing most of the sedentary time in the modern lifestyle, because both the weekly frequency and the weekly duration of exercise time are an order of magnitude less than those for people sitting inactive. This can explain why high amounts of sedentary time produce distinct metabolic and cardiovascular responses through inactivity physiology that are not sufficiently prevented by low doses of exercise. For these reasons, we hypothesize that maintaining a high metabolic rate over the majority of the day, through safe and sustainable types of muscular activity, will be the optimal way to create a healthy active lifestyle over the whole lifespan.

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Abstract figure legend The cause and effect influences impacting what is defined as a health active lifestyle. Beginning at the top left, a sedentary lifestyle (with nearly ubiquitous sitting opportunities) results in infrequent skeletal muscle contractile activity. An ensuing deleterious chain of events creates disease, poor ageing, and ultimately compounding influences to create more sedentary behaviour. In contrast to the sedentary lifestyle, the right side of the diagram shows the chain of events linked to high levels of activity.

Abbreviations DVT, deep vein thrombosis; LIPA, low intensity physical activity; LPL, lipoprotein lipase; LPP1, lipid phosphate phosphatase 1; MVPA, moderate to vigorous physical activity.

Introduction

The purpose of this paper is to provide the historical context and to update a paradigm that has emerged in recent years that continues to shape our thinking about the unique role that muscular activity performs over the whole day in optimizing human physiology and preventing disease (Hamilton *et al.* 2004, 2007, 2014). The intended format is to use language capable of explaining concepts to a general audience, and to put forth new ideas as a way of raising provocative questions that foster rigorous debate and promote scientific endeavour. The article attempts to keep the content conceptually rich and present it as a useful paradigm instead of being descriptive, since there are numerous reviews for that already (Thorp *et al.* 2011; Edwardson *et al.* 2012; Saunders *et al.* 2012; Wilmot *et al.* 2012; Hamilton *et al.* 2014). In so doing, this article could not be replete with the many excellent references by colleagues in the field. My goal here in this article as well as in my own laboratory is to lead the pursuit for developing an approach to *replace as many hours and bouts of unhealthy sedentary time possible with the best type of muscular activity specifically geared toward being safe, feasible, and physiologically effective for optimizing human health in all people, regardless of age and barriers limiting mobility*. This article will outline seven guiding tenets that are intended to help show the way.

A basic yet sound understanding of muscle physiology is critical to keep in mind when thinking about how these tenets provide insights when both comparing different types of activity and identifying the underlying

molecular causal factors. Working muscle fibres must be fuelled, and the time course for changes in contractile activity is very dynamic. The magnitude of change in the energetics and biochemistry of a muscle fibre moving from an inactive to a recruited state (or vice versa) is as large a difference as is seen in biology. Cellular signals impacted by contractile activity drive numerous metabolic and cardiovascular responses. For example, when rats were experimentally made to become more inactive throughout the day, and also when they started moving again, there were changes in the activity of dozens of genes regulating diverse processes (Bey *et al.* 2003). And during that time, specific biochemical pathways that determine the fate of fat and plasma cholesterol were changing more than any other known processes (Bey & Hamilton, 2003), and probably also innumerable other biological processes still needing to be carefully studied. There will probably also be many adaptive benefits specific to the molecular responses that extend beyond the acute time frame by maintaining habitually high levels of contractile activity throughout the day. This fundamental background also impacts pragmatic issues needed to understand the dose–response and time course relationships for how to optimize human movement for promoting better health. This emerging field concerned with reducing sedentary time is largely based on suggestions that a high frequency and duration of movement may produce sizeable health gains, even though the category of activity is not strenuous. This would be especially impactful if effective, low effort and safe muscular activity could be performed with high durations and frequency in a more

universal way than the traditional models of how to exercise.

There is not space to discuss here in detail the molecular mechanisms or growing list of health conditions resulting from the lack of skeletal muscle contractile activity. However, there is a plethora of publications explaining the role of physical activity on dozens of conditions. The early bed-rest studies certainly set the expectation for rapid deterioration in cardiovascular health, for muscular atrophy and for other aspects of impaired human performance. From the whole continuum of evidence, from the controlled cause-and-effect studies in rodents focused on how inactivity physiologically impacts health-related proteins regulating metabolism up to the epidemiological observations about routine sedentary behaviours of the human lifestyle such as watching television, one can most definitely conclude that good health requires a high frequency and duration of daily contractile activity. It is important to keep in mind that this is a young field and the list of conditions negatively impacted by sedentary behaviour may still be growing. This list could include obesity, metabolic syndrome risk factors, diabetes, fatty liver disease, cardiac health, peripheral artery disease, deep vein thrombosis, some cancers, inflammation, muscle atrophy, mood and multiple cognitive changes. Some of our most prevalent, costly and unsustainable healthcare problems share common root causes related to inadequate duration of skeletal muscle contractile activity and are, thus, potentially preventable by a major shift from living most of the day with an inactive muscle metabolism towards a greater reliance on active muscle metabolism.

The key physiological premise

As a result of signals related to skeletal muscle contractile activity and metabolism, the body is constantly sensing its internal environment every minute of the day and responding one way or another to whether or not we are sedentary or active. Some of the most potent mechanisms regulating disease susceptibility proteins (such as those for lipoprotein metabolism and mitochondrial function) are regulated by inactivity (generally when sitting) because the body needs frequent muscular activity throughout the day. In our society, many people are living without the benefits of enough muscle metabolism for the majority of the waking day, as evidenced from wearable devices capturing sedentary time (Spittaels *et al.* 2012; Loprinzi, 2013; Schuna *et al.* 2013; Hamilton *et al.* 2014). Thus, *the ultimate goal is development of a solution involving long durations of muscular contractile activity frequently throughout the whole day.*

A fundamental concept of muscle physiology is the specificity principle, which states that the molecular stimuli and physiological benefits invoked by muscular

activity are specific to the dose and type of activity. Therefore, it is critical to understand the dose–response relationships between varying doses and types of human muscular activity with the bodily response and health effects. Herein lies one of the driving factors in the development of the field of inactivity physiology. Over a decade ago, we started introducing the molecular contrasts between ‘inactivity physiology’ vs. ‘exercise physiology’ (Hamilton *et al.* 2004) and introducing multiple expressions like ‘sitting too much is not the same as exercising too little, either behaviourally or physiologically’. A specific recommendation based on sound muscle physiology is crucial, and it must be a safe, effective solution for all types of people.

A unique goal of inactivity physiology is to improve health outcomes by greatly increasing levels of physical activity in all people, even those who cannot or will not engage in the classical recommendations for moderate to vigorous physical activity (MVPA). If this goal is accomplished, the impact can be far reaching. Development of an effective solution must be based in part on novel insights about the physiology of *how muscular activity* impacts risks caused by prolonged sitting. This has been extremely challenging since sedentary time has been a monumental part of life in the modern world. *The holy grail of healthy active living would come from a breakthrough discovery for how to safely replace most of the sedentary time with physical activity in everyone, regardless of age and current health status.*

In this article, I provide seven tenets for moving beyond association studies or basic physiology studies to integrating human behaviour with easy to understand physiological principles in order to better understand a much-needed scientific approach producing safe and effective active lifestyles.

The seven guiding tenets in the quest for a solution to the problems caused by sedentary time

The concepts are integrated as part of a paradigm and to assist the development of research hypotheses and identification of a worthy solution. The first four tenets were listed formally in 2007 (Hamilton *et al.* 2007), in part described even before that (Hamilton *et al.* 2004). Tenets 5–7 are summarized here for the first time to guide the research going forward.

Tenet 1: sedentary time is surprisingly hazardous to human health in many ways

This was proposed as a hypothesis to encourage more research to test whether or not high amounts of sitting time might be a risky behaviour (Hamilton *et al.* 2004, 2007). At the time, most of the research focus had been on adding exercise on top of the normal lifestyle. However, we

had been noticing remarkably large molecular responses in pre-clinical animal models during inactivity that were not evident during exercise. The exposure rate to the risk of sedentary time is high because people of all ages and demographics sit or are not moving for a large amount of time each day (Craft *et al.* 2012; Levine, 2015; Spittaels *et al.* 2012; Loprinzi, 2013; Schuna *et al.* 2013). To the extent that this tenet is true and owing to the magnitude of the effect, the majority of people are in serious need of a healthy active lifestyle more than previously realized. One area where this hypothesis has been tested the most concerns the doubling in the risk for type 2 diabetes and metabolic syndrome risk factors to sedentary behaviour, even when adjusting for BMI and MVPA (Edwardson *et al.* 2012; Wilmut *et al.* 2012; Hamilton *et al.* 2014). Compounding this problem is the fact that two-thirds of the entire population is overweight or obese already, and there is an expanding population of elderly sedentary people with pre-existing chronic disease. However, one implication to all of this negative news that we have tried to emphasize is the flip side to interpreting the same data; once an effective behavioural solution is discovered, it will be a genuine novel breakthrough capable of creating an enormous positive impact. We and others have tried to also explain consistently in scientific articles (Bey *et al.* 2003; Hamilton *et al.* 2004, 2007; Healy *et al.* 2007; Zderic & Hamilton, 2012; Hamilton *et al.* 2014), lectures, and to the media that *because prolonged sedentary time is surprisingly hazardous to health, logically this must also mean that some type of high duration and frequent muscular activity capable of replacing the large amount of sedentary time must also be surprisingly beneficial for promoting good health.*

Tenet 2: sedentary time is a distinct behavioural class from the time spent engaged in traditional MVPA recommendations

We found that this is most clearly understood with general audiences when using the following phrase: *'too much sitting' (actually, contractile inactivity) is not the same as too little exercise.* Exercise in this case is the narrowly defined type of physical activity recommended by the current physical activity guidelines. Using more technical language, this tenet raised the hypothesis that the various times that people spend sitting inactive or participating in MVPA-based leisure-time physical activity are distinct and totally different classes of behaviour, with distinct determinants and independent effects on risk for disease. This concept has been studied the most by researchers in the past decade because it was stated as a hypothesis suitable for epidemiological studies.

30 min is 1/48th of the day. Adding 30 more minutes of physical activity 5 days per week, in the form of MVPA in bouts of at least 10 min, has been widely

recommended. At the behavioural level, observational association studies (Burton *et al.* 2012; Craft *et al.* 2012; Finni *et al.* 2014; Kozey-Keagle *et al.* 2014) using a variety of measurement techniques have concluded that even in the individuals who exercise beyond twice the recommended 150 min week⁻¹, sitting time and the total daily non-exercise activity were not different from those who rarely exercised. Considering that 30 min is only 1/48th of the day and people are often sitting for over 70 h week⁻¹, this finding that the amount of MVPA hardly makes a dent in the massive amount of sedentary time should not be surprising. Of course, the large amount of sedentary time in people's lifestyle displaces an equally large amount of non-exercise physical activity, and the associated contractile activity and energy demand for human movement throughout the day. Even a person who jogs 20+ miles over ~200 min week⁻¹ is also likely to engage in ~15-fold more time doing other physical activity when not jogging (Craft *et al.* 2012). Physical activity is defined by the NIH and WHO and classical citations (Caspersen *et al.* 1985) as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level at rest. That definition is so clear and widely used that it does not need modification. Yet a simple point that is seemingly lost by many and causing conceptual problems related to tenet 2 is that physical activity exists on a continuum and the most abundant type of physical activity is low intensity physical activity (LIPA). Logically, therefore, inactivity is the absence of activity, not just the absence of one type of activity that is less frequent and more intense (MVPA). The public and scientific progress would be well served to avoid creating confusion and pseudo-debates not only by correctly defining sedentary according to the Latin root (*sedere* means to sit) as we explicitly first noted a decade ago (Hamilton *et al.* 2007), but also by following closer the historically accepted definition of physical activity. To understand the large amount of epidemiological and behavioural research related to tenet 2, it will be helpful to appreciate the effects of the total time and frequency of meaningful muscular activity over the course of the whole day.

Tenet 3: the specificity principle – the molecular stimuli and physiological benefits invoked by muscular activity are specific to the dose and type of activity

This is arguably the most fundamental concept needed to understand how to best perform muscular activity for obtaining the desired responses. By linking the specificity principle with a good understanding of physiology, it is possible to begin to understand the immediate benefits of muscular movement throughout the day, as well as the adaptive responses accumulating over time. This principle

is critical for developing high quality studies to determine dose–response relationships. Athletic training for different sports has always been based on the knowledge that people should train specifically for how they compete.

It was not until 2004 that we were in a position to need to explain this concept within the framework of a new paradigm. However, already by that time we had been starting to see that for some key cellular and molecular factors important for disease risks (Hamilton *et al.* 1998; Bey *et al.* 2001, 2003; Bey & Hamilton, 2003), it was necessary to distinguish the responses of inactivity physiology *versus* classical exercise physiology. And we are probably still at the early stage for seeing how surprisingly necessary it is to have a high frequency and high duration of muscular activity throughout the day in order to promote optimal regulation of diverse categories of genes and proteins ranging from lipid regulation by lipoprotein lipase to genes involved in the regulation of inflammation, glucose regulation, hemostasis, etc. In the past decade, we have begun to see from studies using inclinometers that the average person sits down a little more than 50 times per day (Craft *et al.* 2012), while the accelerometry data reveal that the most natural form of non-exercise walking is in short spurts at a slow speed (Schuna *et al.* 2013). By 2007 (Hamilton *et al.* 2007) and 2014 (Hamilton *et al.* 2014), we had begun to describe the logical implications and how it makes no sense to assume people expect to insert a bolus of muscular activity from two to four sessions per week of MVPA-style exercise to gain all of the same immediate and adaptive benefits derived from hundreds of bouts of muscular activity frequently spread throughout each day.

Interestingly, the most recent federal guidelines for physical activity currently in the USA removed the requirement for any specific frequency of physical activity. In theory, someone can perform 75 min of vigorous activity on the weekend and meet the recommendation to be classified as sufficiently physically active. In fact, the guidelines have always encouraged not breaking up the activity, and have explicitly required that the MVPA be performed in bouts lasting longer than 10 min to count. I speculate that as the field advances, the contrast between the two sets of recommendations for sedentary behaviour and MVPA will continue to expand. Given the specificity principle, this growing contrast is probably a wise and good thing for people who adhere to both, because they can achieve benefits from qualitatively distinct sets of cellular processes promoting good health.

Deep vein thrombosis (DVT) is an example for understanding how this *whole day approach to frequent muscular movement* throughout the day may be the most direct way to prevent a potentially lethal condition (Zderic & Hamilton, 2012; Howard *et al.* 2013). Immobilization of the leg muscles and low rates of muscular blood flow, including during prolonged sitting, is a cause of

DVT within the veins deep in the leg muscles. Taking one other specific cellular example, the expression of a multifunctional gene, *LPP1* (lipid phosphate phosphatase 1, which has a documented potential role in countering haemostasis, cancer and inflammation), in human and rodent skeletal muscle is rapidly reduced by a large amount within the first day of inactivity (Zderic & Hamilton, 2012). And those early preliminary studies provided evidence to support the hypothesis that *LPP1* expression will remain low throughout about 2 weeks of prolonged sitting, regardless of whether or not an hour of intense daily exercise is performed. In summary, the specific signals harming the body caused by prolonged sitting are ideally counteracted by abundant activity throughout the whole day.

One potential naïve misperception for the public, which should be easy to counteract if experts are clear about it, is that eliminating sedentary time is just a stepping stone to ‘real exercise’ only for people who cannot do intense MVPA. First of all, elimination of the majority of the sedentary time in the waking day would raise the total muscular activity time to a mighty high level. Secondly, if the non-sedentary activity was even close to approaching 2-fold resting metabolic rate (2 METs), the cumulative energy expenditure would far exceed the prescriptive levels of $8 \text{ kcal kg}^{-1} \text{ week}^{-1}$ that the MVPA recommendations are explicitly targeting. At 2 METs ($\sim 2 \text{ kcal kg}^{-1} \text{ h}^{-1}$), and a sitting time of $\sim 70 \text{ h week}^{-1}$ in healthy adults, there is an enormous opportunity for raising the total cumulative energy demand if a feasible means of eliminating a large amount of sedentary time was to be developed safely for the sedentary population.

A quantitative summary of the second and third tenets for general audiences could be illustrated as shown. From the above discussion, *the obvious conclusion is that exercising 3 times per week to gain 3 h of muscular activity is far from the perfect antidote for problems caused by typical amounts of sedentary behaviour, which is commonly associated with sitting down ~ 350 times per week to induce $\sim 70 \text{ h}$ of muscular inactivity.* These proportions are illustrated in Fig. 1. For complete original results, see Figs 2 and 3 in Craft *et al.* (2012) and Fig. 4B in (Hamilton *et al.* 2014).

What about the intensity of physical activity? First, if possible people should ideally be encouraged to do both a small duration and low frequency MVPA (just like the current guidelines have been doing for years) and a high duration of lower effort physical activity spread frequently throughout the whole day. The optimum intensity and mode for the high duration activity is dependent in part upon fatigue, feasibility, safety and physiological effectiveness. This issue is obviously one of the most distinct reasons why this paradigm is far different from the classical research focused only on brief amounts of

MVPA. Second, there is more than one way to define intensity. Is it based on the absolute minute by minute oxygen consumption, the relative metabolic effort of the individual, the amount of movement captured in an accelerometer, or most directly to what physical activity is defined by the EMG level of the working muscle? And since most researchers rely on indirect tools, the public certainly has trouble with intensity-based recommendations. In some ways, the long-standing 3 MET threshold for the border between light and moderate intensity has served science well. Now there is a growing number of researchers also using a 1.5 MET threshold for sedentary and light. The dose–response between health-related outcomes and types of activity ranging from complete inactivity (< 1 MET in most adults) to the ~1.5–2.0 MET range has not received enough research, and desperately warrants more. The type of standing as when one is standing to work at a desk is generally less than 1.5 METs, and may be of marginal cardiometabolic benefit if more movement is necessary.

Third, the interaction between intensity, frequency and duration is highly inter-related. The standard in exercise physiology is to match either the duration or the total caloric volume when comparing intensity. This is reasonable, but one has to thoughtfully consider

that in the real world, the amount of time spent in moderate activity is vastly less than the time at lower intensity muscular activity. So what does a comparison of 2 METs vs. 5 METs mean when the daily duration achieved at 2 METs is more than 10-fold greater than the higher intensity? The specificity principle (tenet 3) submits that these are such different stimuli on the physiological systems of the body that they each may be of benefit through different molecular pathways. For example, there are rapid and transient rises in metabolic rate and blood flow that stimulate fat and carbohydrate oxidation during the moments a muscle is contracting (tenet 5). Therefore, it is theoretically possible using this example that these ‘immediate benefits’ are happening 10 times more often at the lower intensity because the muscular activity is taking place 10 times more often. But the higher intensity may also stimulate some other distinct processes. In this way, the unique benefits of both ends of the intensity range of activity would be complementary for rounding out a more complete health portfolio. We need to avoid ridiculous assertions that one healthy lifestyle factor (physical activity) can replace another factor (healthy diet or smoking), when in reality, distinct categories of behaviour cannot replace one another.

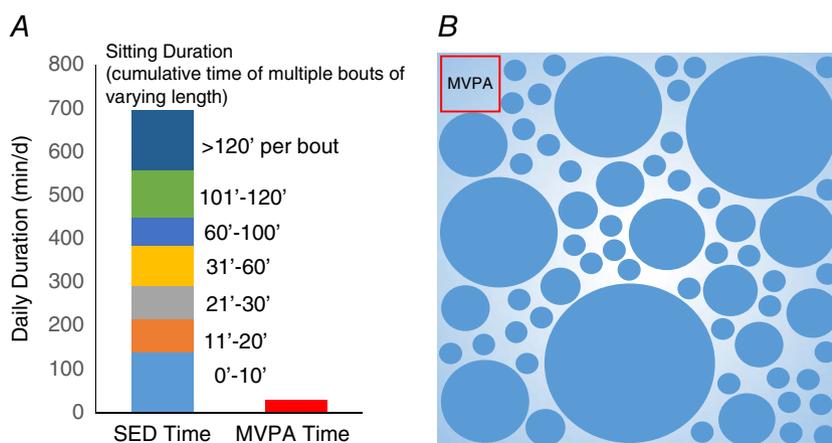


Figure 1. Volume of total daily sitting duration

A, quantitative data for the daily time spent sitting of a typical sedentary person as measured with a device that measures upright vs sitting time and also the time engaged in ambulation at different intensities. From this, the cumulative daily time spent sitting was approximately 11.5 h, which was caused by dozens of sitting bouts. **B**, the relative volume of time occupied by each sitting bout, the number of daily sitting bouts in a sedentary person, and the relatively small influence that a bout of recommended MVPA has on either sedentary parameter (bout number or total sedentary time). The total volume of the square represents the total awake time. The round balls represent individual sitting bouts that fill up approximately 68% of the waking day. Because these sitting bouts are spread throughout the entire day and often without consistent patterns due to variations in lifestyles of different people, the sitting bouts in this graph are not depicted in any order. Instead the panel emphasizes how sedentary time fills up the waking day in variable ways. The theme when interpreting these data is the realization that there is an amount of sitting time spread throughout the whole day in various bout lengths and various patterns that creates an enormous challenge in reducing sedentary time and requires highly focused efforts on this problem. And, because of the need to specifically eliminate as many sedentary bouts and as much sedentary time as is safely possible, innovative behavioural strategies will produce results far different from the longstanding MVPA recommendations.

Tenet 4: in people who do not already exercise, it logically follows that further increased rates for disease and mortality cannot be caused by additional exercise deficiency. The potential benefits of replacing large and frequent amounts of sedentary time with safe and achievable physical activity should be widely discussed, without delay

The shape of the dose–response curve between fitness/activity and mortality or disease outcomes has long suggested that the major public health benefits are by getting the most inactive people to move more rather than making average people exercise (Hamilton *et al.* 2004). And if the ability to effectively replace sedentary time with a large amount of safe muscular activity is *not* developed, the trajectory for growing numbers of sedentary people with multiple chronic diseases will continue to escalate in the wrong direction. Technological advances and other causes promoting sedentary behaviour seem to continually make growing numbers of people sit more. Thus, society may not have yet reached the pinnacle of seeing the full range of poor health caused by the impact of sedentary time on preventable conditions (such as type 2 diabetes, cardiovascular disease, obesity, metabolic syndrome, DVT, fatty liver disease, dementia and some cancers). Type 2 diabetes is already on an unsustainable trajectory for management by our healthcare system. The root cause is in large part the sedentary lifestyles we choose, with seven studies (see Hamilton *et al.* (2014) for a review and discussion) showing that prolonged TV watching more than doubles the risk for diabetes (even after accounting for MVPA and BMI). Thus this tenet was raised out of dire concern for the possible growing numbers of people unaware of the potentially insidious effects of sedentary living. One of the most frequent questions by public health advocates has been, if daily sedentary time has been a ubiquitous health hazard, why are we just learning about it now? A fundamental goal of good public health research is to identify previously unrecognized, yet common causes of disease. I have frequently shown conclusion slides in my talks for general audiences to make this point, by using the analogy with smoking and tobacco. The point is, for much too long, there was also not a dire concern raised for the many people unaware of health hazards caused by smoking. I show a picture of the now familiar rectangular warning label eventually required in advertisements, which states ‘Warning: smoking may be hazardous to your health’. Then I show another picture with the word ‘sitting’ to replace the word ‘smoking’. One early print advertisement even shows a young Ronald Reagan with a large stack of gift wrapped cartons, while stating, ‘I am sending Chesterfields to all of my friends. That’s the merriest Christmas any smoker can have.’ As with smoking, I seriously doubt long-term randomized controlled trials will be funded to induce

more sedentary time to study hard outcomes. But the short-term studies are clear already: even a single day of inactivity is potentially unhealthy (Bey *et al.* 2003; Bey & Hamilton, 2003; Stevens *et al.* 2011; Dunstan *et al.* 2012; Saunders *et al.* 2012; Zderic & Hamilton, 2012; Duvivier *et al.* 2013; Howard *et al.* 2013; Duvivier *et al.* 2017).

Tenet 5: the rapid time course of health-related responses to physical inactivity/activity is in large part because of the direct effects caused by muscle contractile activity throughout the day

Nothing else than contractile inactivity/activity comes close to having a greater instantaneous effect on variations in metabolic rate throughout each hour of the day. Skeletal muscle undergoes greater swings in metabolic rate from moment to moment than any other tissue type in the body. As introduced above, the metabolic rate of a muscle fibre at rest is quite low, but can rise 50- to 100-fold immediately upon activation. As soon as a muscle starts contracting, ATP (the cellular energy currency) demand rises immediately by a large amount. Blood flow and other support processes can also change at the onset and cessation of contractile activity in order to support the energy demand of the working fibres. These factors help to explain why after experimentally decreasing normal spontaneous ambulatory contractile activity, my laboratory found rapid and large changes in lipoprotein lipase (LPL) activity in tandem with slower extraction of blood triglyceride locally in oxidative muscle, and significant decreases in high-density lipoprotein (HDL) cholesterol (Bey *et al.* 2003). That is likely to be only the foreshadowing of many other responses where LPL may play a role in explaining the phenotypes caused by sitting inactive or by high amounts of low effort contractile activity, since low LPL is associated with several phenotypes important for disease risk. Experimentally reduced LPL activity in oxidative muscle caused by acute contractile inactivity was related to blunted removal of fat from the blood locally by oxidative muscle and reduced HDL plasma concentration in rats (Bey *et al.* 2003). And we also found that LPL in human skeletal muscle was highly correlated with triglyceride ($r = -0.98$) and HDL size ($r = +0.90$ with) and several other lipoprotein parameters (Harrison *et al.* 2012). Interestingly, intense cycling exercise to fatigue did not raise skeletal muscle LPL (Harrison *et al.* 2012). A decrease in LPL in skeletal muscle of insulin-resistant humans at risk for diabetes has been mechanistically linked to reduced signalling for mitochondrial biogenesis (Morino *et al.* 2012). Finally, LPL activity in human plasma causes a potent signalling response to produce anti-inflammatory responses (Ziouzenkova *et al.* 2003). Taken together, there are rapid and functionally important effects of changes in contractile activity of slow oxidative

muscle (soleus) mediated through LPL activity over the course of a normal day. In contrast, intense running did not increase either LPL mRNA or LPL activity in the rat soleus muscle. However, when rats performed prolonged slow ambulatory activity for several hours, there was a large increase in LPL activity in the soleus, completely reversing the decrease produced by prolonged contractile inactivity (Bey *et al.* 2003). An important hypothesis is that this LPL response is mediating multiple novel health-related responses, by virtue of pleiotropic effects of LPL on lipoprotein metabolism, mitochondrial function and anti-inflammatory protection.

Even at rest when muscle metabolism is not optimal, most (~80%) of the insulin-dependent glucose utilization after eating is determined by muscle metabolism. The ability of muscle to optimally metabolize glucose (and fat) is central to many aspects of disease prevention. In theory, raising the metabolic rate of muscle substantially for many hours throughout each day (as is best done by contractile activity), including but not limited to after eating meals, would be able to optimize the role of muscle in health promotion. The first study to document large effects on insulin sensitivity caused by sustaining low intensity contractile activity most of the day instead of prolonged sitting offered two other surprising twists (Stevens *et al.* 2011). Given that it was using a single day model, the time course was too rapid to be explained by body composition, which offers hope to people seeking an immediate benefit of insulin sensitivity without weight loss requirements. Secondly, the acute inactivity physiology effects were evident despite the fact that most volunteers were relatively fit and regular exercisers (Stevens *et al.* 2011), which provides experimental causal evidence supporting the hypothesis in the second tenet. Since then there have been other experimental studies of acute inactivity compared to light activity spread over the day in a variety of types of people (Dunstan *et al.* 2012; Saunders *et al.* 2012; Duvivier *et al.* 2013, 2017; Howard *et al.* 2013), supporting the second and fifth tenets. With regards to improved glucose metabolism during acute intermittent walking over the postprandial period, Dunstan *et al.* (2012) found that walking briskly (a moderate pace that was as fast as overweight-obese people could walk) was not superior to slower walking when matched for time (and thus more calories were burned at the higher intensity). One group found in both healthy controls (Duvivier *et al.* 2013) and people with diabetes (Duvivier *et al.* 2017) that a large duration of low intensity activity spread throughout the whole day was superior to intense endurance cycling that was matched for total energy demand. However, it should be emphasized that as far as we know, none of the published proof of principle studies have yet documented a safe and fatigue-resistant behavioural approach capable of eliminating a large duration of

sedentary time throughout the day such as what is needed for claiming victory in a likely public health solution (tenet 7).

The potent and quick momentary responses to muscular activity lead to one seminal conclusion as the science progresses in the future: *public health campaigns should eventually provide people with a rich sense of 'metabolic awareness' about the concept that 'the body constantly senses and responds to movement vs inactivity', in tandem with behavioural strategies promoting the ability to take full advantage of every opportunity to move more.* And this is likely to be good news for all kinds of people, because evidence indicates that the immediate benefits of movement are independent of other more intractable long-term issues such as weight loss and cardiorespiratory fitness.

Tenet 6: the role of local contractile activity and muscle specificity

One of the most useful concepts in muscle physiology is that once a motor neuron is stimulated, the affected muscle fibres respond with close to an all-or-none type of contractile phenomenon. Because of this, the force output within large weight-bearing muscles of the leg are graded mostly by recruitment of more motor units, not by a graded intensity within the individual fibres. This fundamental physiology regarding how the body works when we move helps us to understand why 'light' physical activity can produce powerful changes in cellular signalling, metabolism and health outcomes. At the level of the fibres contributing to low effort activity such as strolling during indoor walking, the rise in energy demand and fuel supply to the working muscle cells is far from being a light stimulus.

Phenotypic diversity between different fibre types means that all muscles are not created equal, nor do they respond similarly to physical activity. There is a heterogeneity for the metabolic proteins, fatigue resistance, and threshold for activation during graded contractile intensity. In each of our studies in rats, the *local* contractile activity within the slow-twitch oxidative muscle appears to be most important for explaining the reason for maintaining a high duration of daily low intensity physical activity in young adults (Hamilton *et al.* 1998; Bey *et al.* 2003; Hamilton *et al.* 2014) and with ageing (Bey *et al.* 2001). It is not known if this holds true across species, because the heterogeneity between muscle regions (deep red oxidative *vs.* superficial white glycolytic) is more evident in rats than in humans. However, we hypothesize that the metabolic responses in relatively fatigue-resistant slow-twitch oxidative skeletal muscle has a dominant role in combating the diseases associated with too much sitting.

Tenet 7: we do not need a band-aid. We do need a revolutionary breakthrough! For a genuine public health solution to address the complete problem of sedentary inactivity, a solution that is potent and safely attainable by most everyone is needed

Major advances moving forward can occur. But to get there and see the breakthroughs for what they are, we need to know what goals we are looking for. The seven tenets and concepts in this paper hopefully point a way there. I see three things the experts should be open to considering for making discoveries needed to find that solution scientifically, but also to get the buy-in from the public to adopt a major behaviour change. First, we cannot trivialize the process by aiming low or wasting limited resources on descriptive guesses about what to study without a good understanding of how the body works from translational insights. For some people, it seems for some reason that the goal of research has been to learn how little movement people can do and still get some benefit (e.g. micro-breaks at the end of the hour). However, for the person who has recently been diagnosed with a life-threatening condition or is on the pathway for losing eyesight or a leg because of diabetes complications, the more significant question should probably not be how little they can do to help their situation, but how much can be done to maximize health.

Second, we need to avoid the confusion in the public health messaging caused by pseudo-debates appearing too frequently with the nutritional recommendations. Thus, we should work cooperatively and embrace solutions that raise activity over a large amount of the day and are safe and practical for the whole population, including the elderly, obese and people with chronic conditions. A challenge of our time is how to make all types of people become much more active. This is especially important and challenging for the people who account for most of the healthcare costs and need an activity-based solution the most.

Third, the experts and funders cannot be cynical, just because prior public health failures are many. History is filled with seismic shifts in the right direction for public health just when gloom and doom seemed everywhere. A systematic review of the existing interventions to reduce sedentary time reported on 51 studies (Martin *et al.* 2015), with the meta-analysis showing only 22 min day⁻¹ reduction of the intervention group. Humans have inadvertently manufactured an insidious problem of metabolic inertia that has caused us to live with a stalled metabolic rate for the past several decades. Ironically, sedentarism is a type of inertia, which is defined as 'a body at rest tends to stay at rest'. But it is absolutely possible for major scientific breakthroughs to provide momentum for the solution. And with that momentum, bodies will be put in motion and tend to stay in motion, both throughout the waking day and for healthy ageing.

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Additional information

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