

Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes

Short title: Sedentary behaviour and type 2 diabetes

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Abstract

Our modern day society encompasses an ecological niche in which sedentary behaviour, labour saving devices and energy dense foods have become the new reference of living. We now spend more time sedentary, defined as sitting, than in all other activities combined. It has recently been confirmed that the consequences of our modern chair-dependency are substantial and a direct contributing factor to the ever increasing epidemic of chronic diseases witnessed within industrialised environments. Epidemiological evidence - from both cross-sectional and prospective observational studies - has indicated that the time spent in sedentary behaviour is a distinct risk factor for several health outcomes; including type 2 diabetes, insulin resistance, all-cause and cardiovascular disease mortality, depression and some types of cancer. Importantly, these detrimental associations remain even after accounting for time spent in moderate-to-vigorous physical activity; with the strongest and most persistent associations seen between sedentary time and type 2 diabetes. Importantly, experimental studies have started to confirm the observational associations, with mounting evidence showing that breaking prolonged sitting time with light ambulation is an effective strategy for improving postprandial glucose regulation. Indeed, there is even emerging evidence showing that simply substituting sitting for standing regularly throughout the day may be of sufficient stimulus to improve glucose regulation. We highlight some of the key definitions, issues and evidence underpinning the link between sedentary behaviour and chronic disease in order to better inform clinicians and patients about the importance of incorporating reduced sitting time into type 2 diabetes management and prevention pathways.

Keywords: Sedentary behaviour; type 2 diabetes; glucose; insulin

Introduction

Modern society now encompasses an ecological niche in which sedentary behaviour (sitting), labour saving devices and energy dense foods have become the new reference of living. Despite this shift being accompanied by undoubted improvements in living conditions, it has unintentionally created a mismatch between our evolutionary history and the environment for which humans have adapted. The modern day human evolved to be bipedal, ambulatory and upright, thus allowing a competitive environment in which hunting, foraging, migration and agriculture could flourish. Put simply, humans were not designed to sit all day. However, with little creativity, a person can now eat, work, shop, bank and socialise without having to leave the comfort of their chair. The consequences of our increasing chair-dependency are now recognised as a unique health hazard that has greatly contributed to the modern epidemic of chronic disease, in particular cardiovascular disease and type 2 diabetes mellitus (T2DM). Here we highlight some of the key definitions, issues and evidence underpinning the link between sitting and chronic disease to inform clinicians and patients about the importance of reducing sitting behaviour as an additional element in the T2DM management or prevention pathways.

Definition of sedentary behaviour

The term sedentary behaviour (from the Latin word sedere, ‘to sit’) is defined as “any waking behaviour characterised by an energy expenditure ≤ 1.5 METs (multiples of the resting metabolic rate) while in a sitting or reclining posture” [1]. One MET is the energy cost of resting quietly, often defined in terms of oxygen uptake as $3.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ [2]. Whilst the energy threshold at which sitting becomes non-sedentary may be of academic interest, the current 1.5 MET threshold remains controversial and problematic. For example, many common sitting-based activities fall outside this threshold, including driving and some computer games [2,3]. This, coupled with the fact that it is often impractical to measure energy expenditure, means that sedentary behaviour should be operationally defined as any sitting behaviour conducted outside of structured exercise. During sitting or lying, leg muscles, the largest muscle mass in the body, are not stimulated. Conversely, when standing, even if relatively still, a large proportion of the body’s musculature system is under tension and activated as it serves its anti-gravity functions [4]. Therefore, any standing activity, even at low energy expenditure, can be defined as non-sedentary.

The definition of sedentary behaviour is fundamentally different to that of physical inactivity; the latter of which is most commonly used to categorise those not achieving the minimum recommendations of moderate-to-vigorous intensity physical activity (MVPA) (150 minutes per week). Thus it is possible for someone not to take part in any formal MVPA, yet engage in very little sedentary behaviour due to occupational demands such as a nurse or waiter. Conversely, a health conscious individual who complies with current recommendations for health by exercising for 30 minutes five days a week may still be highly sedentary if they spend the rest of their time in a desk bound job and sit for the remainder of their leisure or transport time. This distinction is at the heart of the sedentary behaviour paradigm and the subsequent evidence is highlighted below.

Prevalence of sedentary behaviour

Within modern society, many adults now spend the majority of their waking hours sedentary, a figure that far surpasses the hunting, gathering and migratory patterns of our ancestors. Based on objectively measured data, the average adult spends 55 to 70% of their waking time sedentary [5], with those who have a high risk of chronic disease at the upper end of this range [6]. As such, assuming 8 hours of sleep daily, individuals typically spend around 11 hours per day sedentary. The majority of the remaining time is spent in light activity, with 10% or less dedicated to MVPA. A typical pattern of behaviour for an individual with established dysglycaemia, gained from an objective accelerometer measurement device is displayed in Figure 1.

Sedentary behaviour and energy balance

Although there is some overlap in energy expenditure between sitting and standing activities, it is invariably true that most standing activities have slightly higher energy expenditures than sitting activities. Indeed when undertaking the same task, such as typing, standing will always have a higher energy expenditure than sitting due to greater muscle activation, largely driven by posture-controlling muscles. Therefore it is plausible that over recent decades, the reduction in standing and light movement throughout daily living and occupational activities has contributed in some part to the modern obesity epidemic. Indeed, it has been shown that the reduction in occupational energy expenditure over the last 5 decades directly maps onto the obesity epidemic in the United States [7]. Others have also noted that the sales of energy saving devices, that have helped facilitate increased sedentary behaviour, correlate with increasing levels of obesity, whereas changes in energy intake do not [8]. Even in today's environment, differing occupational roles can have a substantial impact upon

daily energy expenditure. For example it has been hypothesised that compared to a highly sedentary desk bound worker, a waiter or hospital nurse could expend up to 800 kcals per day more [9]. Even a fairly modest increase in energy expenditure of 200kcal per day would equate to over 4kg weight loss over the course of a year assuming unchanged energy intake (based on a 90kg male) [10]. Given these findings it is highly likely that in order to effectively target the obesity epidemic, innovative solutions are needed to promote reduced sedentary behaviour in our occupational and home settings.

Sedentary behaviour and T2DM

Detailed reference to the deleterious health consequences of prolonged sedentary time were made at the beginning of 18th century by the father of occupational health, Bernardino Ramazzini, who noted “...those who sit at their work and are therefore called 'chair workers,' such as cobblers and tailors, suffer from their own particular diseases ... [T]hese workers ... suffer from general ill-health and an excessive accumulation of unwholesome humors caused by their sedentary life ...” [11]. However, it was not until the 1950s that this link was formally quantified in the pioneering work of Dr Jeremy Morris [12]. Although the primary focus of the study was to investigate differences in physical activity levels, this seminal epidemiological study, published in the Lancet, found that workers who spent the majority of their day sitting (London bus drivers and mail sorters) were at higher risk of cardiovascular events than employees who stood more frequently and engaged in ambulation while working (ticket collectors and postal workers) [12]. This was the first study to show the detrimental impact of high levels of sedentary time on health. However, it was not until the early 2000’s that researchers began to focus their attention on outcomes associated with sedentary behaviour that were independent of the time spent in MVPA.

Over the last decade, several reviews have pooled the expeditious accumulation of epidemiological evidence - from both cross-sectional and prospective observational studies – to indicate that the time spent in sedentary behaviours is a distinct risk factor for several health outcomes [13]; including increased risk for all-cause, CVD related and all other causes of mortality [14-16], depression [17] and some types of cancer; including colon [18], endometrial [19], and ovarian [20].

However, the strongest and most consistent evidence linking sedentary behaviour to adverse health risk is for T2DM and insulin resistance, which also includes the clustering of metabolic risk factors such as hypertension, dyslipidemia and obesity [21,22]. We have previously shown in a meta-analysis that sedentary behaviour is strongly associated with the risk of developing T2DM, both

through standard and Bayesian analytical techniques [16]. Here, compared to those that were least sedentary, those with high levels of sedentary behaviour had over twice the risk of developing T2DM. Importantly, these results remained after levels of MVPA were taken into account, highlighting the independent nature of the association between sedentary behaviour and health. This is consistent with another meta-analysis that demonstrated that every two hour difference in TV viewing time, a surrogate marker of sedentary behaviour, was associated with a 20% difference in diabetes risk, a 15% difference in cardiovascular morbidity and a 13% difference in all-cause mortality [23]. This study also clearly demonstrated the dose-response nature of the association. Evidence for the link to diabetes prevalence and incidence is strengthened by studies that have used objective measures of sedentary behaviour and found associations with glucose levels [24,25]. The evidence appears particularly compelling for those with a high risk of, or diagnosed, T2DM where objectively measured sedentary behaviour is strongly associated with markers of insulin resistance, even after adjustment for MVPA [26] and markers of adiposity [27,28]. We have also shown that the association between sedentary time and insulin resistance in a high risk cohort remains consistent across a common genetic polymorphism in the *PPARG2* gene [29]. This is significant because the polymorphism imparts a strong modifying effect on the effect of MVPA with the wild type displaying only weak associations between MVPA and insulin resistance [29], this further supports the independent role of sedentary behaviour in regulating metabolic health.

The strong and consistent epidemiological evidence from both cross-sectional and prospective data linking sedentary behaviour to health, particularly T2DM and insulin resistance, has permitted the generation of hypotheses that are now starting to be pursued in experimental studies. This is important as more empirical research is needed across the proximal–distal continuum of risks associated with sedentary behaviour in order to better understand biological pathways potentially linking prolonged sitting to chronic diseases.

Experimental studies

Experimental sedentary behaviour interventions differ from traditional bed rest studies in that they frame the research question in relation to the environmental “norms” placed on human behaviour within modern society. In essence, either approach is justified depending on the question asked, but in the context of this review, only the sedentary behaviour approach has the ability to influence future behavioural therapies. This places exorbitant sitting as the default behaviour and several

studies have investigated the impact of reducing prolonged sitting (through standing or light movement) on health outcomes [30-33] .

For example, the impact of breaking prolonged sitting with 2 minute bouts of light or moderate walking every 20 minutes over a 5 hour period has been examined in overweight and obese adults. Postprandial glucose and insulin area under the curves were significantly reduced by 24% and 23% respectively with light intensity walking breaks with similar results seen for moderate walking. These findings were confirmed in another small randomised controlled cross-over study [31]. This study, conducted in healthy, normal weight adults, compared the effects of prolonged sitting (9 hours), continuous physical activity combined with prolonged sitting (1 x 30 minute bout of walking), and regular light walking breaks on postprandial metabolism (walking for 1m40s every 30 minutes). The results showed that regular activity breaks (with a 39% reduction in the glucose area under the postprandial curve) were more effective than continuous physical activity at decreasing postprandial glycaemia levels [31]. This points to the added value of incorporating regular breaks to sedentary behaviour throughout the day, rather than in a single bout, which has also been noted in other experimental [34] and epidemiological [25,28,35] studies.

There is also emerging evidence that increased standing, without walking, may also have a significant impact on metabolic health. Thorp et al. (2014) recently examined, through a randomised design, the impact of alternating 30 minute bouts of sitting and standing through the provision of sit-stand desks compared to prolonged sitting, on metabolic health in overweight/obese office workers during an 8 hour working day. The glucose area under the postprandial curve was 11% lower in the sit-stand condition, although the difference in insulin failed to reach significance [36]. This is consistent with a non-randomised office-based study which found that glucose levels were reduced by 43% following an afternoon of standing compared with seated computer work [37]. However, not all standing based studies have yielded significant results, particularly in healthy younger adults [38,39].

Importantly, we recognise that some individuals, especially those with chronic disease, are wheelchair bound and thus will be excluded from the potential metabolic benefits elucidated in the experimental research to date. We are currently investigating whether the metabolic benefits of breaking sedentary behaviour regularly throughout the day can also be achieved with light-intensity arm and back exercises.

In conclusion there is consistent experimental evidence that breaking sitting behaviour with light ambulation is an effective strategy for improving glucose regulation with some further encouraging evidence that simply substituting sitting for standing throughout the day improves glucose regulation, particularly when undertaken in an office environment in overweight and obese adults [40]. Ongoing research through international collaborations is now beginning to extend these experimental sedentary methodologies by examining older adults and those with existing dysglycaemia.

Guidelines

Contrary to definitions of MVPA, established or agreed criteria for defining categories of sedentary time for health recommendations or agreed targets for intervention are lacking. That said, broad guidelines promulgating general non-specific reductions in sitting time are beginning to emerge in physical activity recommendations (including the UK [41,42] and Australia [43]). Moreover, using much of the evidence highlighted above, a group of experts was recently convened to draw up the first ever guidance for office workers and occupational health. This guidance states that during working hours, office workers should initially aim to incorporate 2 hours of standing (assuming a full working day), working up to 4 hours over the longer term [44]. Assuming an average working day of 8 hours, this equates to spending half our working lives standing. Unlike purposeful MVPA, which generally necessitates time away from the primary tool of productivity (i.e. computer), the provision of sit-stand desks can facilitate reduced sitting and increased standing without impacting productivity; for example, standing does not affect typing speed [45]. Indeed, productivity over the longer-term may actually be improved as regularly substituting sitting for standing has been shown to reduce feeling of fatigue and musculoskeletal complaints [46,47], the latter of which is the primary source of lost productivity within the workplace.

More broadly, the link between sedentary behaviour and health has displayed a clear dose-response relationship. Based on both epidemiological and early experimental work, reducing sitting time by approximately 60 minutes per day is likely to be around the minimum needed to gain clinical benefit, which greater reductions resulting in greater health gain [23,30,48,49].

Implications for the treatment and prevention of T2DM

Given the mounting evidence for the importance of reducing sedentary behaviour as a therapeutic target, particularly in the promotion of metabolic health, there is a need to consider how this evidence

can be incorporated into diabetes prevention and treatment pathways. To date, behaviour change interventions have lagged behind the epidemiological and experimental evidence, however there are a couple of key considerations which warrant further discussion. In particular, care is needed regarding how interventions aimed at reducing sedentary behaviour are integrated alongside those for increasing regular MVPA.

Undoubtedly, MVPA and physical fitness have unequivocal benefits in the prevention and management of T2DM. For example, supervised exercise training studies have consistently been shown to reduce HbA1c by around 0.7%, with reductions closer to 1% observed for studies that have employed higher doses of intervention [50]. Exercise training is even beneficial in those with peripheral neuropathy through enhanced glycaemic control and nerve regeneration [51-53]. In addition, cardiorespiratory fitness remains one of the most powerful determinants of an individual's risk of early all-cause or cardiovascular mortality, including those with T2DM [54,55]. Therefore, it is vital that interventions or public health messages that are aimed at reducing sedentary behaviour are run in parallel to those for MVPA.

However, when measured objectively, less than 5% of the population undertake 30 minutes of MVPA on at least days 5 of the week [56-58], a figure that is likely to be even lower in those with chronic disease. Therefore regular purposeful MVPA is likely to be on the outer reaches of the normal habitual day to day experiences for the majority of individuals with chronic disease. Consequently, it is behaviourally implausible that inactive and sedentary individuals will easily tolerate interventions that are aimed at replacing sedentary time with MVPA, the traditional focus of public health interventions. As such, interventions that focus specifically on reducing sedentary behaviour may be more effective than those designed to increase physical activity [59]. In general, individuals may do better using a stepped approach whereby the first step is aimed at reducing sitting time through increasing standing or light ambulation [60]. If tolerated, light ambulation could then turn into purposeful movement. We have modelled the likely health benefits of these approaches. Re-allocating 30 minutes of sedentary time into light movement was associated with a 5% increase in insulin sensitivity in those with a high risk of T2DM, whereas reallocating sedentary time with 30 minutes of MVPA was associated with an 18% improvement in insulin sensitivity [61] (see Figure 2). Therefore, increasing MVPA should remain a strong focus and end point of behavioural intervention, however we should also recognise that substantial benefits may be gained by substituting sedentary time for light-intensity activity and that for many individuals, particularly those with chronic disease, this may be the option that is best tolerated.

Conclusions

The large amount of time spent sitting in modern environments has emerged as an independent risk factor for chronic disease, and is associated with glucose regulation and insulin resistance in the general population, those with a high risk of T2DM and those diagnosed with T2DM. Experimental evidence has confirmed that regularly breaking sitting time with standing or light walking substantially reduces postprandial glucose levels, suggesting a new behavioural target for those with a high risk of, or diagnosed, T2DM. As the sedentary behaviour research matures, future translational work is likely to have a substantial public health impact and inform future policies on the optimal approaches to reducing prolonged sitting time as part of an integrated lifestyle promotion pathway. In the meantime, a good starting point is the behavioural rule of thumb that states: when sitting, stand where possible; when standing, walk or employ purposeful movement where possible.

Conflict of interest

There are no conflicts of interest

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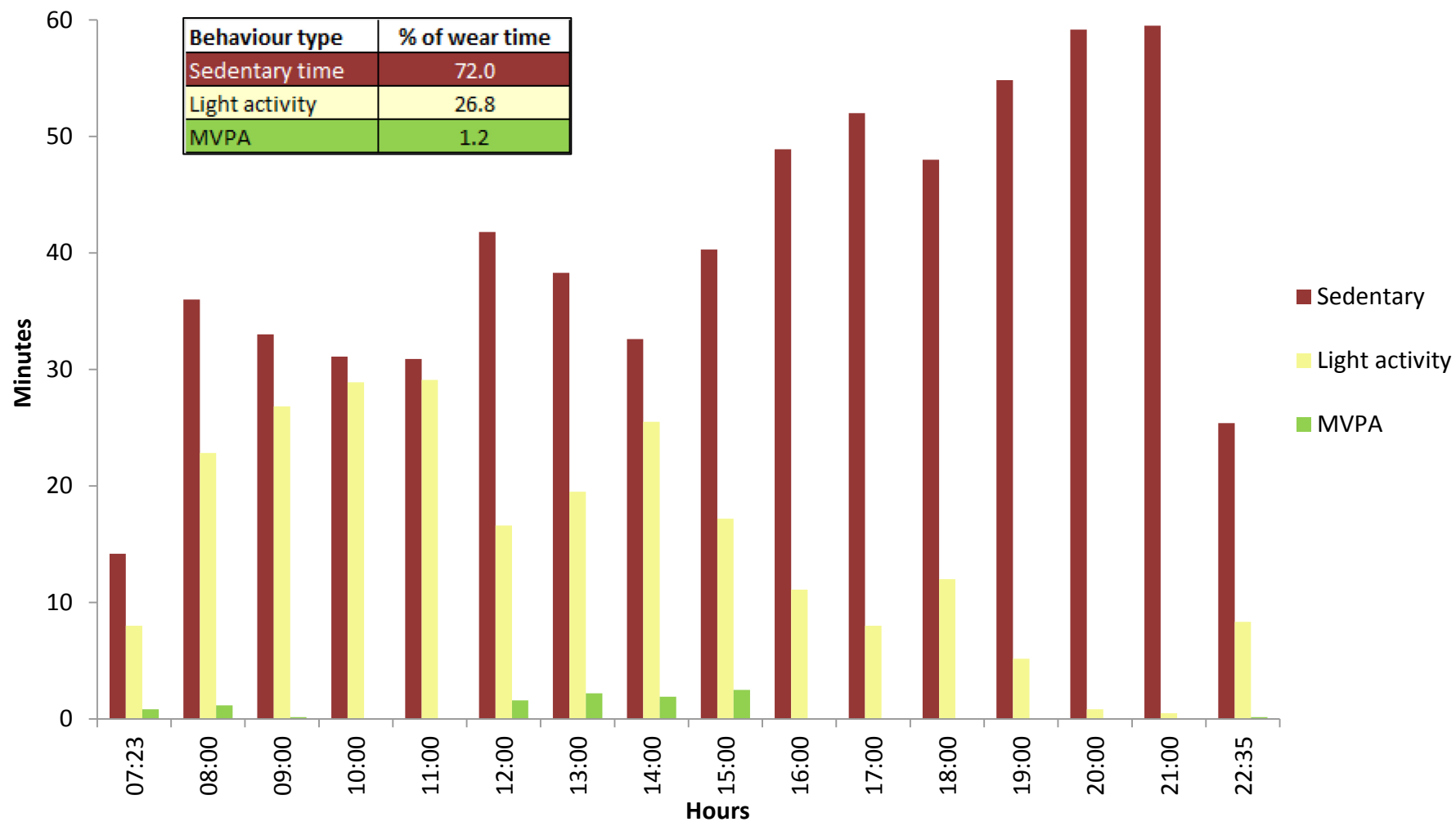
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Figure 1. A typical, hour by hour accelerometer trace from a dysglycaemic individual, showing sedentary time (red bars), light activity (yellow bars) and MVPA (green bars)



MVPA: Moderate-to-vigorous physical activity

Figure 2. The potential impact on insulin sensitivity of re-allocating 30 minutes of sedentary time to either light activity or MVPA (Taken from Yates *et al.* 2015 [48])

