# Sit less and move more for cardiovascular health: emerging insights and opportunities

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Abstract | Sedentary behaviour — put simply, too much sitting, as a distinct concept from too little exercise — is a novel determinant of cardiovascular risk. This definition provides a perspective that is complementary to the well-understood detrimental effects of physical inactivity. Sitting occupies the majority of the daily waking hours in most adults and has become even more pervasive owing to the COVID-19 pandemic. The potential for a broad cardiovascular health benefit exists through an integrated approach that involves 'sitting less and moving more'. In this Review, we first consider observational and experimental evidence on the adverse effects of prolonged, uninterrupted sitting and the evidence identifying the possible mechanisms underlying the associated risk. We summarize the results of randomized controlled trials demonstrating the feasibility of changing sedentary behaviour. We also highlight evidence on the deleterious synergies between sedentary behaviour and physical inactivity as the underpinnings of our case for addressing them jointly in mitigating cardiovascular risk. This integrated approach should not only reduce the specific risks of too much sitting but also have a positive effect on the total amount of physical activity, with the potential to more broadly benefit the health of individuals living with or at risk of developing cardiovascular disease.

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Sedentary behaviours that typically involve long periods of sitting during waking hours might have physiological consequences that are distinct from those of a lack of moderate–vigorous-intensity physical activity, often referred to as exercise. Many adults spend more than half of their waking hours sitting, with this pattern further amplified by the coronavirus disease 2019 (COVID-19) pandemic[1]. In this Review, we make a case for an approach to preventing and managing cardiovascular disease that involves 'sitting less and moving more'. This approach can build on the well-established role of exercise in cardiovascular disease prevention and rehabilitation. Observational and experimental evidence on the likely cardiovascular health benefits of reducing and regularly interrupting sitting time are the basis of this approach along with an emerging understanding of the biological mechanisms that point to a rational basis for doing so.

Physical inactivity, defined as a level of activity that is insufficient to meet current physical activity guidelines[2], has long been known to be a major contributor to the risk of cardiovascular disease. Physical activity levels are lowest among older adults (aged ≥65 years), who are also at the highest risk of cardiovascular disease compared with all other age groups[3]. New ways to understand and influence the health risks of physical inactivity are now emerging. The lack of regular physical activity and the large amounts of time spent in sedentary behaviours (defined as any waking behaviour characterized by an energy expenditure <1.5 times the basal metabolic rate, that is, 1.5 metabolic equivalent of task (MET), while in a sitting, lying or reclining posture)[2] can have both distinct and interrelated influences on cardiovascular risk. Furthermore, adults can meet or exceed public health guidelines for physical activity but also spend most of their waking hours sitting (FIG. 1).

Particularly informative insights have come from advances in the device-based measurement of physical activity. Over the past seven decades of physical activity and health research, the observational studies and intervention trials relied on participant reports of exposures and outcomes. Measurement error was a widely recognized problem, limiting what could be inferred from the research findings. Technological advances have overcome many of the inherent limitations of the previous generation of studies and the more precise measurements available are delivering new research insights. Small, wearable, research-grade devices (accelerometers) can now provide data across an entire day (FIG. 2). Findings from studies that used device-based

**Key points**

- Sedentary behaviour — that is, too much sitting, as a distinct concept from too little exercise — has been shown through observational and experimental findings to adversely affect cardiovascular health.
- Observational evidence shows that sitting occupies the majority of adults' waking hours and excessive sitting contributes to cardiovascular risk, particularly among individuals who do not meet the current physical activity recommendations.
- Prolonged, uninterrupted sitting detrimentally affects several biological processes related to cardiovascular risk; high levels of sitting displace total physically active time, negating the cardiovascular benefits of skeletal muscle activity.
- New evidence suggests the potential for broad cardiovascular health benefits through reducing and interrupting sitting time through practical and acceptable approaches involving 'sitting less and moving more'.

measurement capacities have provided a more precise and comprehensive perspective than self-reported measures of the total spectrum of activity by identifying the large amounts of time that most adults spend sitting, in light-intensity physical activity (both of which were poorly characterized by self-reported measures), and in moderate-intensity and vigorous-intensity physical activity.

Of note, device-based measures have reaffirmed that high levels of sedentary behaviour are unfavourably associated with overall physical activity levels[4]. Specifically, a strong inverse relationship exists between sedentary behaviour and total physical activity, with the strongest associations observed for light-intensity physical activity[4]. This inverse relationship highlights a fundamental principle that any time spent in sedentary behaviour displaces time spent in total physical activity. The effects of the COVID-19 pandemic have amplified the importance of addressing the balance between sedentary behaviour and physical activity. For example, early evidence suggests that risk mitigation strategies, such as social distancing and 'stay at home' orders, have resulted in large reductions in physical activity and substantial increases in sedentary time, particularly among individuals who were previously physically active[5,6] (FIG. 2a). The extraordinary challenges and remaining uncertainties imposed by the global COVID-19 health crisis have the potential to further escalate the pandemic of physical inactivity and sedentary behaviour (FIG. 2a). Therefore, we have a strong imperative, perhaps more than ever, to find ways to create a healthier balance through sitting less and moving more[1,7].

FIGURE 2b shows examples of daily patterns of sitting time and movement assessed by an activity monitor device and illustrates how these device-based measurement capacities can provide new perspectives through more powerful and finer-resolution lenses. These devices have considerably sharpened the scientific focus that can help to characterize daily activity with higher degrees of precision, particularly with new insights into the under-recognized role of sedentary behaviour (not only the total time spent sitting but also the patterns of sitting time, including brief, physically active interruptions).

## Observational evidence

Understanding the health risks of sitting has consolidated rapidly over the past two decades in a broad body of scientific findings[8]. Sedentary behaviour is now explicitly identified in new clinical and public-health guidelines on reducing sitting time in addition to increasing physical activity and exercise[9–11]. Notably, the first recommendation of the 2018 US Physical Activity Guidelines for adults (18–64 years) and older adults (≥65 years) emphasizes the promotion of sitting less and moving more for all and that doing some physical activity is better than none, while those who sit less and do any amount of moderate–vigorous-intensity physical activity gain some health benefits[10]. Below, we elaborate on this evidence and highlight the population health implications of excessive sitting for cardiovascular outcomes.

Population-based studies using self-reported measures suggest that daily sitting time in adults typically ranges between 5 and 8 hours[12–14]. The examination of trends over the past 10 years suggests that self-reported sedentary time has increased by around 1 hour per day[15,16]. In the USA, findings from the NHANES study revealed that, based on self-reported measures, the proportion of adults who do not adhere to physical activity guidelines and sit for >6 hours per day increased from 16.1% in 2007–2008 to 18.8% in 2015–2016 (REF.[15]). These findings are plausible and are in accordance with commonsense observations of social, technological and other changes currently influencing the lifestyle of large numbers of adults. However, device-based estimates from

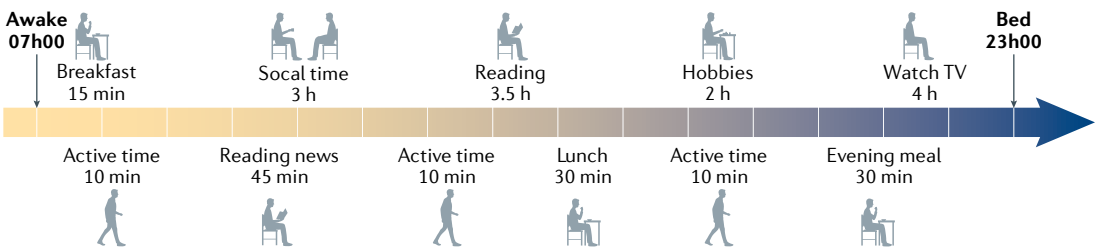


Fig. 1 | **Daily activities that involve sitting.** For non-working adults who sleep 8 hours in a 24-hour cycle, the remaining waking hours (16 hours) can be occupied with various recreational activities and activities of daily living. In this hypothetical example, these adults can be considered physically active according to current physical activity guidelines because they accumulate up to 30 minutes of physical activity over the course of the day. However, these individuals can also spend multiple hours (14.5 hours) sitting during meal times, socializing and enjoying recreational activities. Therefore, despite meeting current physical activity guidelines, non-working adults can spend up to 90% of their remaining waking hours sitting. This substantial sitting time is not an atypical pattern for many older adults and might be characterized as being 'active but also highly sedentary'[104]. This example highlights the importance of not only targeting time spent being active but also reducing the time spent sitting during waking hours (or 'sitting less and moving more').

**Sedentary behaviours**
Specific categories of sedentary behaviour, the most common include sitting during television viewing, video game playing and computer use (collectively termed 'screen time'), sitting in automobiles and sitting while reading.

**Sitting**
A position in which an individual's weight is supported by the buttocks rather than the feet and in which the back is upright.

**Physical activity**
Any bodily movement produced by skeletal muscles that results in energy expenditure.

**Exercise**
A component of physical activity; refers to activity that is planned, structured and repetitive for the purpose of improving or maintaining one or more components of physical fitness.

**Physical inactivity**
A level of weekly physical activity that is insufficient to meet present physical activity and health guidelines.

**Physical activity guidelines**
Recommendations from authoritative health-care bodies for practitioners and the public, specifying the type, amount and intensities of physical activity from which worthwhile health benefits should accrue.

**Metabolic equivalent of task**
(MET). Unit corresponding to multiples of the resting metabolic rate in humans (3.5 ml $O_2$ per kg/min).

**Lying**
Being in a horizontal position on a supporting surface.

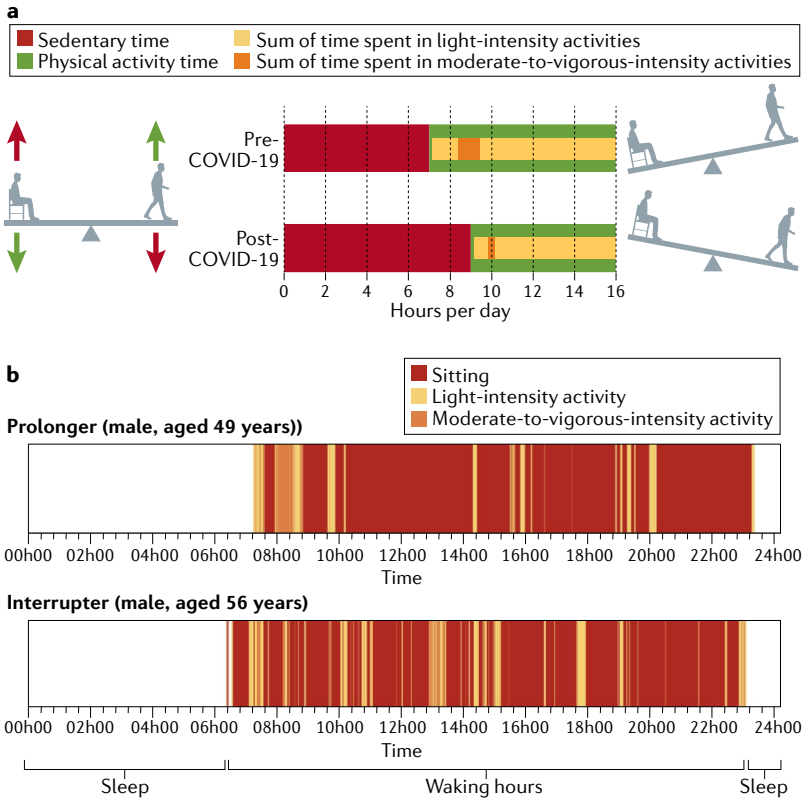


Fig. 2 | **Single-day activity data generated from the activPAL device. a** | Device-based measures have confirmed the fundamental principle that any time spent in sedentary behaviour displaces time spent in total physical activity (the sum of the activity of all intensities). Consequently, the only countermeasure to sitting during waking hours must be through increases in physical activity (irrespective of intensity). The 'balance' (that is, the equivalent time spent sitting and in total physical activity) might be shifted if increases in sitting lead to the displacement of total physical activity (left panel; red arrow indicates a less-desired balance). By contrast, increases in total physical activity invariably lead to decreases in sitting time (green arrow indicates a more-desired balance). In the hypothetical example (right panel), we illustrate how changes resulting from coronavirus disease 2019 (COVID-19) restrictions might result in a reversal of the balance in a physically active person, whereby opportunities for undertaking both light-intensity and moderate–vigorous-intensity physical activity might have diminished, leading to increased sitting time[1]. These COVID-19-induced changes can subsequently result in the less-desired balance (that is, more sitting than total physical activity). **b** | Two participants from the AusDiab3 study who have similar total sitting time (~13 hours) and moderate–vigorous physical activity (~0.7 hours) but contrasting patterns of sitting time (red) and physical activity (light-intensity physical activity (yellow) and moderate–vigorous-intensity physical activity (orange)). These individuals are classified as either a 'prolonger' or an 'interrupter'. These data show the full 24-hour period for the waking hours. Of note, the pattern of the red, yellow and orange bars indicates that the 'prolonger' sits for extended periods and infrequently interrupts this sitting time with physical activity, whereas the 'interrupter' accumulates a similar amount of sitting time during waking hours but has a higher frequency of transitions from sitting to physical activity.

Reclining
A body position between sitting and lying.

Device-based measurement
Measures of physical activity based on hip-worn, wrist-worn or thigh-worn devices from which minute-by-minute measures of bodily acceleration and posture can be captured across a whole day.

population studies and large cohorts show that the mean daily sedentary time in adults might actually be much higher than indicated in previous estimates that were based on self-reports and, indeed, could be in the range of 7.7–11.5 hours per day[17–19]. This increased sitting time has substantial implications for cardiovascular risk.

Findings from numerous observational studies using device-based measurements have provided important insights into the health consequences of these large volumes of sitting time. For example, in a geographically diverse, biracial US sample of middle-aged and older adults (≥45 years), device-measured total sedentary time and prolonged, uninterrupted sedentary bouts were both associated with an increased risk of all-cause death after consideration of the influence of physical activity[20]. Further examination of these data modelled the influence of replacing sedentary time with more active time[21]. This analysis identified a substantial reduction in all-cause mortality in less active adults in the study but not among those who were more active (who engaged in a total of 3.5 hours per day of light-intensity and moderate-intensity physical activity). Concordant findings emerged from the study of older women (mean age 79 years) participating in the Women's Health Initiative (a racially and ethnically diverse study sub-cohort aged 63–97 years). Both high sedentary time and longer mean sedentary bout durations were associated with the risk of cardiovascular disease in a dose–response manner[22]. This association remained after accounting for health status, physical function and cardiovascular disease risk factors, including moderate–vigorous physical activity[22]. A further examination of this cohort found a relationship between sedentary time and the prevalence of diabetes mellitus[23]. Together, this set of prospective epidemiological findings that are based on device-derived measures emphasize the importance of less time spent in sedentary behaviours and of shorter sedentary bouts in those aged ≥45 years.

Despite the effects of sedentary behaviour on total physical activity levels, studies in young (mean age 22 years) and older (mean age 64 years) adults have shown that device-measured sedentary time is inversely associated with measures of cardiorespiratory fitness and functional fitness, even after adjusting for time spent in moderate–vigorous-intensity activity[24,25], suggesting that the health risks associated with sedentary behaviour might be attenuated by increasing fitness levels. Furthermore, evidence from the Danish Health Examination Survey indicates that the influence of self-reported sitting time on cardiorespiratory fitness is most pronounced in individuals with low levels of physical activity[26]. Epidemiological evidence suggests that cardiorespiratory fitness moderates the association between sedentary behaviour and cardiometabolic risk factors, such that weaker associations are observed in individuals with higher fitness levels[27,28]. Only high levels of cardiorespiratory fitness (>43.3 ml/kg/min in men and >35.2 ml/kg/min in women) seem to fully mitigate the deleterious associations between high levels of sitting time and cardiometabolic risk[27]. Although an increase in fitness levels might lead to greater improvements in cardiovascular risk factors, the activity levels required to achieve this improvement are high. Furthermore, frequent, brief physically active interruptions to sedentary time have the potential to lead to improved fitness and health.

The evidence described above is part of a broader body of work reported over the past decade, with accumulating, highly informative evidence from prospective epidemiological studies documenting that long periods of time spent in sedentary behaviour can lead to adverse health outcomes — particularly for cardiovascular disease. The comprehensive review undertaken by the 2018

Table 1 | **Effects of sedentary behaviour on health outcomes**

| Health outcomes | Level of evidence for increased risk with sedentary behaviour | | |
|---|---|---|---|
| | Association | Dose–response | Variation in association by physical activity |
| All-cause mortality | Strong | Strong | Strong |
| Cardiovascular disease mortality | Strong | Strong | Moderate |
| Incident cardiovascular disease | Strong | Strong | NR |
| Incident type 2 diabetes mellitus | Strong | Limited | NR |
| Weight status | Limited | Limited | NR |

Based on data from the 2018 Physical Activity Guidelines Advisory Committee Scientific Report[29]. Grading of the magnitude and precision of effect criteria used by the 2018 Physical Activity Guidelines Advisory Committee. NR, not reported.

Vigorous-intensity physical activity
Physical activities of >6 metabolic equivalent of tasks.

Total physical activity
Sum of time spent in physical activity of light, moderate and vigorous intensity.

Light-intensity physical activity
Physical activities of 1.5 to <3.0 metabolic equivalent of tasks.

Sedentary behaviour
Any waking behaviour characterized by an energy expenditure of <1.5 metabolic equivalent of tasks, while in a sitting, reclining or lying posture.

Self-reported measures
The type of exposure assessment that has been most typically used in epidemiological studies on physical activity and health outcomes, often using 1-week recall via a self-completion survey or interview.

Total sedentary time
Time spent in sedentary behaviour that can be inferred from minimal measured movement based on an accelerometer reading; for example, the total time accumulated below a defined threshold.

Moderate-intensity physical activity
Physical activities of 3 to <6 metabolic equivalent of tasks.

Physical Activity Guidelines Advisory Committee for the second edition of the Physical Activity Guidelines for Americans has been pivotal in synthesizing the evidence in terms of the relationships between sedentary behaviour (at this point in time largely from studies using self-reported measures) and health outcomes in adults[29].

TABLE 1 summarizes the findings from the Physical Activity Guidelines Advisory Committee that are relevant to cardiovascular disease. The main conclusion is that strong evidence is available to support that exposure to high volumes of sitting time significantly increases the risk of all-cause and cardiovascular death and the incidence of cardiovascular disease and type 2 diabetes mellitus[29]. Furthermore, findings from a systematic review and harmonized meta-analysis of accelerometer-assessed sedentary time showed that higher amounts of sedentary time are associated with an increased risk of all-cause death[17]. Conversely, higher levels of total physical activity — regardless of intensity level — are associated with a lower risk of all-cause death[17]. Across increasing quartiles of sedentary time (relative to the first quartile; median range 371–519 minutes per day), the hazard ratios for all-cause mortality were 1.28, 1.71 and 2.63 for the second quartile (469–588 minutes per day), third quartile (542–639 minutes per day) and fourth quartile (624–705 minutes per day), respectively[17]. Relative to the first quartile of total physical activity (53–196 counts per minute (CPM)), the hazard ratios for all-cause mortality were 0.48, 0.34 and 0.27 for the second quartile (134–291 CPM), third quartile (199–371 CPM) and fourth quartile (304–522 CPM), respectively[17].

Further insights from studies using isotemporal modelling approaches indicate that replacing bouts of sitting time (30–60 minutes) with either light or moderate–vigorous-intensity physical activity is associated with reductions in all-cause and cardiovascular mortality and cardiometabolic risk markers, particularly among less-active adults[30–33]. Consistently, stronger associations are seen when sitting time is replaced by moderate–vigorous-intensity physical activity. This association has been confirmed in later studies using device-based measures in older populations aged ≥70 years[34,35]. For example, in a study of >3,000 older men and women, every 30-minute increment per day in light-intensity activity or moderate–vigorous-intensity physical activity was associated with 11% and 36% decreases in the risk of cardiovascular disease or all-cause death, respectively[34]. By contrast, every 1-hour per day increment in sedentary time increased the risk of these outcomes by 33%[34].

## Mechanisms of sitting-related risk

Biological systems related to the adverse health consequences of physical inactivity have been reviewed extensively[36] but less is known about the pathways that underlie the risks of too much sitting. Experimental evidence is beginning to accumulate that elucidates some of the crucial biological associations between sitting time and decreased cardiovascular health. Laboratory studies with healthy and unhealthy adults have experimentally identified the effect of prolonged periods of sitting, with or without brief, physically active interruptions, on cardiovascular risk factors. The scientific rationale for these experimental approaches is underpinned by the crucial principle that, by definition, physical activity (that is, any bodily movement produced by skeletal muscles that requires energy expenditure) must be the countermeasure to sitting during waking hours. The relevant pathways are multifaceted, function across major biological systems and interact to increase the overall risk of cardiovascular disease (FIG. 3).

***Vascular function.*** Vascular function is affected during prolonged periods of sitting, particularly in the lower limbs[37] (FIG. 3). A meta-analysis of 17 studies showed that prolonged sitting led to an acute impairment of vascular function as measured by flow-mediated dilation (standardized mean difference (SMD) –0.84)[38]. By contrast, breaking up prolonged periods of sitting with physically active interruptions significantly improved lower-limb vascular function (SMD 0.57)[38]. Reductions in blood flow and shear stress have been attributed to acute, sitting-induced vascular dysfunction. Indeed, a lower blood flow and shear stress decrease the availability of nitric oxide and increase the production of vasoconstrictors, such as endothelin 1, that impair vascular function[39]. Evidence to support these mechanisms comes from trials of interventions that attenuate the reduction in blood flow and shear stress during sitting via lower-limb heating[40], increasing metabolic flow via fidgeting[41] or introducing regular activity interruptions[42,43]. All interventions preserved vascular function.

The mechanisms underlying the reduction in blood flow and shear stress during sitting are probably multifaceted. The diminished muscular activity when sitting, particularly in the large, lower-limb, weight-bearing muscles, and the subsequent reduction in energy demand lead to decreased peripheral blood flow, resulting in reduced shear stress[44]. Additionally, decreases in blood flow and shear stress might relate to prolonged gravitational forces increasing the hydrostatic pressure within the lower limbs, a mechanism supported by observations of increased calf circumference after prolonged sitting, which indicates venous pooling[45]. Sitting-induced increases in muscle sympathetic nerve activity[46] and blood viscosity[47] might also contribute to altered blood flow and shear stress.

Interruptions to sedentary time
Transition from sitting to standing or moving so that prolonged periods of sitting time are regularly interrupted, with observational and experimental evidence suggesting health benefits from doing so.

***Blood pressure.*** The reduction in metabolic demand and blood flow during prolonged sitting is likely to contribute to acute increases in blood pressure[48], with several, but not all[49], studies reporting reductions in blood pressure when sitting time is interrupted by regular brief bouts of physical activity[50–52] (FIG. 3). The magnitude of the effect of prolonged sitting in increasing blood pressure or the blood pressure-lowering effect of regular physically active interruptions seem to be greater in individuals with existing cardiovascular disease risk factors such as obesity and type 2 diabetes mellitus[48]. The lower metabolic demand of sitting, coupled with reduced levels of vasodilatory metabolites, might lead to vasoconstriction in inactive muscles and, consequently, to increased peripheral resistance and mean arterial pressure[48]. However, these mechanisms underlying the blood pressure-lowering effects of interrupting sitting time remain hypothetical given the current lack of relevant experimental evidence.

Elevated sympathetic nervous system activity might also contribute to acute increases in blood pressure during prolonged sitting[48]. In patients with type 2 diabetes mellitus, prolonged sitting increased plasma noradrenaline levels, with a concurrent increase in blood pressure; interrupting sitting with regular brief bouts of physical activity resulted in blood pressure reductions[50]. These blood pressure variations might be caused by changes in total peripheral resistance owing to the vasoconstricting influence of noradrenaline[53].

In the blood pressure context, the biomechanics of sitting itself might increase the risk of cardiovascular disease. Sitting causes bending and angulation of lower-limb arteries owing to hip and knee flexion, which in addition to contributing to decreased blood flow, can also induce turbulent blood flow and shear-stress patterns[44] (FIG. 3). Importantly, low and oscillatory shear stress can increase oxidative stress and decrease vascular function[54]. Consistent with this perspective, blood flow and shear stress can be lower when lying supine with a bent leg compared with a straight leg[44]. Under these experimental conditions, only the prolonged leg bending resulted in an impairment in vascular function[44]. Furthermore, 3 hours of standing, thereby avoiding arterial bending in the legs, can preserve leg vascular function compared with prolonged sitting[55]. Arterial angulation during sitting might also increase peripheral vascular resistance, contributing to sitting-induced elevations in blood pressure[48].

***Blood glucose levels.*** Postprandial glucose, insulin and triacylglycerol levels in blood are acutely elevated after periods of prolonged sitting (FIG. 3), which might also contribute to the previously described effects of sitting on vascular function because insulin resistance and hyperglycaemia are associated with vascular dysfunction[56]. This sitting-induced metabolic dysfunction is attenuated by regular interruptions with physical activity[57]. A meta-analysis of 37 studies showed that regular interruptions with physical activity during prolonged sitting had a

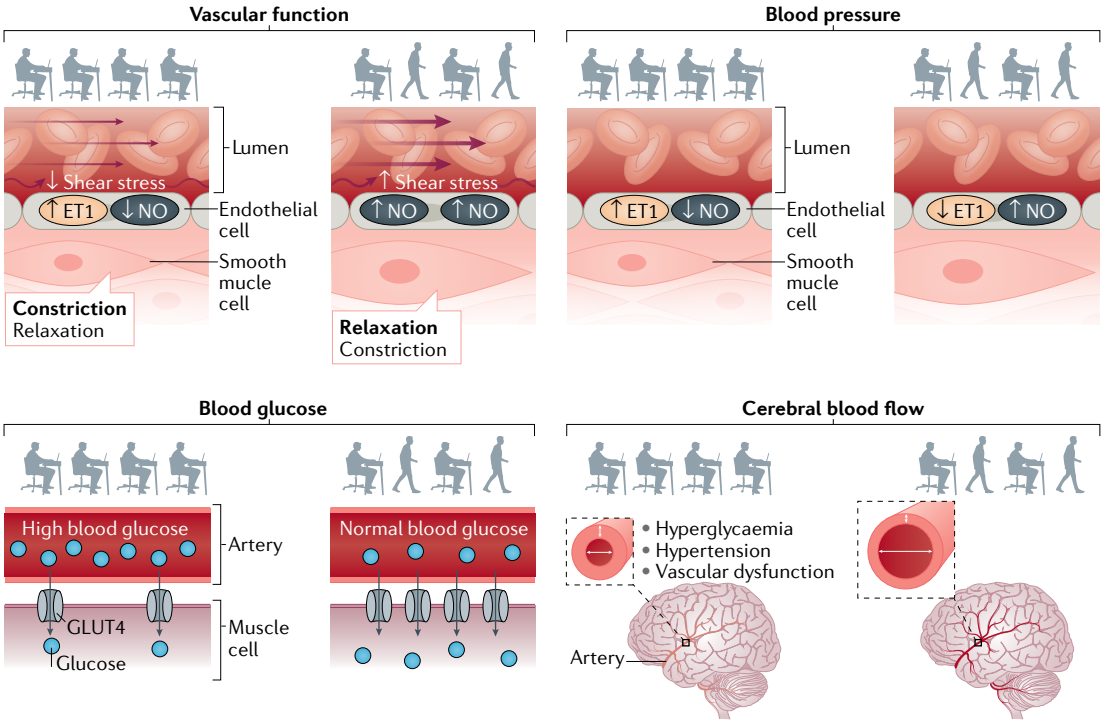


Fig. 3 | **Potential mechanisms for the sitting-induced risk of cardiovascular disease.** Sitting probably acts across multiple biological systems to regulate vascular function (top left), blood pressure (top right), blood glucose (bottom left) and cerebral blood flow (bottom right). Initial evidence suggests that regular physically active interruptions to sedentary time might attenuate these physiological perturbations to reduce the risk of cardiovascular disease. These pathways might interact to increase the risk of cardiovascular disease. ET1, endothelin 1; GLUT4, glucose transporter type 4; NO, nitric oxide.

significant beneficial effect by acutely reducing glucose (SMD −0.54) and insulin (SMD −0.56) levels compared with continuous sitting[57]. Furthermore, individuals at higher risk of cardiovascular disease (physically inactive, type 2 diabetes mellitus and impaired fasting glucose) had greater reductions in glucose levels (SMD −0.62) with regular active interruptions. Although most studies have investigated the acute changes in glycaemic control during a single day of sitting, with or without brief, physically active interruptions, some studies have shown that the improved glycaemic regulation induced by regular active interruptions to sitting persists overnight[58,59].

The primary mechanism potentially explaining the influence of sitting on glucose metabolism relates to glucose uptake by skeletal muscle via insulin-mediated and contraction-mediated pathways[60]. Both pathways result in glucose transporter 4 translocation to the plasma membrane, facilitating glucose uptake and thereby reducing blood glucose levels. Experimental evidence from skeletal muscle biopsy samples has shown that interrupting prolonged sitting with regular active bouts for 1 or 3 days increased the expression of proteins involved in both pathways compared with 1 or 3 days of uninterrupted sitting[60]. Furthermore, physically active interruptions during prolonged sitting lead to the increased expression, in skeletal muscle, of genes related to the regulation of carbohydrate metabolism compared with uninterrupted sitting[61]. Therefore, frequent muscular contractions resulting from physically active interruptions in prolonged sitting might promote increased muscle cell glucose uptake via the increased expression of glucose transporter 4.

Regular, physically active interruptions during prolonged sitting had a small significant beneficial effect by acutely reducing triacylglycerol levels (SMD −0.26) compared with uninterrupted sitting[57]. The smaller effect of physically active interruptions during sitting on triacylglycerol levels compared with the effects on glucose and insulin levels might relate to the delayed activation of lipoprotein lipase after physical activity[62]. Consequently, studies assessing acute effects (single day designs) do not capture the long-term beneficial effect of physically active interruptions during sitting time that have been observed in 2-day or multi-day study designs[57]. Studies in animals have shown that prolonged muscle inactivity lowers lipoprotein lipase activity[63]. Therefore, muscle inactivity while sitting might attenuate the muscle-mediated uptake of fatty acids[64]. Experimental research in humans is required to further explore the cardiovascular-health relevance of this hypothesis. Studies in humans have investigated alternative mechanisms underlying the beneficial effects of physically active interruptions during prolonged sitting on triacylglycerol levels. Lipidomic analysis in patients with type 2 diabetes mellitus showed that regular interruptions to sitting reduced the plasma levels of pro-inflammatory lipids and increased the concentrations of lipids associated with antioxidant capacity compared with prolonged sitting[65]. However, in those who are overweight, physically active interruptions to sedentary time reduced postprandial insulinaemic responses but did not affect adipose tissue gene expression compared with uninterrupted sitting[66].

***Cerebral blood flow.*** Sitting-induced impairments in blood glucose regulation might also affect cerebrovascular function (FIG. 3). Cerebrovascular function encompasses mechanisms that maintain constant cerebral perfusion, preventing ischaemic brain injury and damage[67]. Importantly, impaired cerebrovascular function is involved in diseases such as vascular dementia and stroke[68]. Acute hyperglycaemia has been suggested to reduce regional cerebral blood flow and increase insulin secretion, promoting glucose clearance and creating a glucose nadir[69]. This glucose nadir can impair endocrine counter-regulation to subsequent decreases in glucose, exacerbating hypoglycaemia and impairing vascular function[69]. Given that uninterrupted sitting can induce hyperglycaemia, this process might occur during prolonged sitting periods, leading to vascular dysfunction of cerebral arteries. However, this mechanism, while biologically plausible, requires support from relevant human experimental evidence.

Increases in blood pressure after prolonged sitting might also affect cerebral blood flow. Cerebral autoregulation maintains a constant blood flow despite changes in blood pressure[67]. Increased blood pressure might evoke cerebral vasoconstriction to increase cerebral resistance, maintaining a constant flow of blood. Indeed, in older adults (mean age 78 years), 3 hours of sitting increased blood pressure and cerebrovascular resistance[70]. Increased vascular resistance causes arterial remodelling, reducing lumen size[71], which over time, might reduce cerebral blood flow. Experimental investigations in healthy adults have shown that interrupting prolonged sitting with regular, brief, physical activity bouts can attenuate the reductions in cerebral blood flow velocity induced during prolonged sitting[72]. This benefit might be caused, in part, by alterations in the neural control of the cerebrovasculature. Cerebral blood vessels are innervated by cholinergic fibres, which are stimulated during physical activity, contributing to increased cerebral blood flow[73]. Therefore, frequent physically active interruptions might increase cholinergic activity, thereby maintaining cerebral blood flow[72]. By contrast, the cerebral vasculature is also innervated by sympathetic fibres, which cause vasoconstriction[74]. Given that sitting elevates muscle sympathetic nerve activity[46], prolonged sitting might induce cerebral vasoconstriction, thereby reducing cerebral blood flow. Despite these potential mechanisms, studies in older adults (mean age 78 years) showed no change in cerebral blood flow after prolonged sitting[70]. Age-related decreases in cerebral blood flow attenuating absolute blood flow reductions might explain the lack of cerebral blood change after sitting in older adults[70]. Importantly, however, chronic exposure to acute sitting-induced reductions in cerebral blood flow might contribute to this age-related decline[72]. Further human experimental studies are now needed to elucidate these potential mechanisms.

***Inflammation.*** Increased systemic inflammation caused by prolonged sitting might broadly contribute across different systems to factors that can increase the risk of

cardiovascular disease. For example, chronic low-grade systemic inflammation is associated with the development of cardiovascular disease[75]. Cross-sectional studies have shown that increased amounts of sitting time are detrimentally associated with levels of C-reactive protein and IL-6 in the plasma[76–78]. Furthermore, as mentioned above, prolonged sitting time can induce postprandial hyperglycaemia and postprandial spikes in glucose have been shown to increase the levels of circulating markers of inflammation[79]. Although experimental research to date on prolonged sitting and inflammation is limited, one study showed that interrupting sitting with high-intensity exercise lowered the acute increase in salivary IL-8 levels induced by uninterrupted sitting[80].

Inflammation might also contribute to sitting-induced impairments in vascular function given that inflammatory markers are associated with reduced nitric oxide availability and activate the vascular production of reactive oxygen species[81] (FIG. 3). However, research on this link remains unclear. The oral administration of vitamin C, a reactive oxygen species scavenger, prevented vascular dysfunction after 3 hours of sitting but blood markers of oxidative stress were not measured[82]. Moreover, in another study, the same sitting duration impaired vascular function but no concomitant changes in plasma markers of systemic oxidative stress were observed, suggesting that oxidative stress-independent mechanisms were responsible for the change in vascular function[83]. Finally, the possibility that chronic low-grade inflammation and oxidative stress, resulting in arterial stiffening, might contribute to chronic elevations in blood pressure owing to prolonged sitting remains open to question[48].

***Sitting-induced 'exercise resistance'.*** Prolonged, uninterrupted sitting might further increase the risk of cardiovascular disease by promoting the development of sitting-induced 'exercise resistance', involving reductions in the typical responses observed after acute exercise[84]. Acute exercise lowers plasma glucose, insulin and triglyceride levels. However, 4 days of prolonged sitting prevents these expected beneficial postprandial responses to acute exercise[84,85]. Furthermore, despite the known blood pressure-lowering effects of acute exercise, when this activity is followed by prolonged sitting, the benefits are attenuated[52]. Alternatively, the blood pressure-lowering response to acute exercise is increased if sitting is interrupted with brief bouts of physical activity[52]. In this context, sitting might contribute to the risk of cardiovascular disease in two ways: through the adverse processes described above that occur during sitting and by blunting the cardioprotective benefits of exercise.

***Future directions.*** Experimental evidence relevant to understanding the mechanisms by which sedentary behaviour affects the major pathways implicated in cardiovascular disease is, at present, largely restricted to the acute effects of prolonged sitting. Extension of this work to longer-term mechanistic investigations is warranted. Furthermore, the majority of studies have been conducted in healthy populations and often include only male participants. Therefore, sex-specific differences are unclear, although some differences are evident for vascular function and blood pressure[52,86]. Women have demonstrated a greater protection from acute sitting-induced vascular dysfunction[86] and an improved acute blood pressure-lowering response to physically active interruptions to prolonged sitting[52]. Given the links between the biological pathways underlying the influence of sitting on cardiovascular risk factors (FIG. 3), experimental research also needs to consider an integrated approach that will enable the identification of potential adverse synergies.

## Sedentary behaviour reduction trials

The heightened interest in sedentary behaviour as a public-health issue has stimulated the conduct of >30 controlled trials of interventions to reduce sedentary behaviour in adult populations since 2003 (REF.[87]). These interventions can be categorized into three types: environmental interventions designed to make changes to a particular behavioural setting (for example, sit–stand workstations in workplaces), educational and motivational interventions that target the behaviour of the individual (for example, smartphone apps and educational programmes), and multicomponent interventions that incorporate both environmental and educational or motivational components.

A meta-analysis of the findings of trials of sedentary behaviour reduction interventions has identified the high feasibility of changing sedentary behaviour in adults, reporting that the pooled effect of the intervention groups was a significant reduction in daily sitting time of −30.4 minute per day[87]. Environmental interventions yielded the largest reduction (−40.6 minutes per day), followed by multicomponent (−35.5 minutes per day) and behavioural (−23.8 minutes per day) interventions. This new evidence updates and builds on an earlier meta-analysis that reported a high feasibility of change and that interventions that focus solely on sedentary behaviours yield much greater reductions in sedentary time than physical activity interventions or combined physical activity and sedentary behaviour interventions[88].

The observed reductions in sedentary behaviour, particularly for environmental and multicomponent interventions, are clinically relevant because sedentary time has a high inverse correlation with light-intensity physical activity (Spearman's $\rho = 0.98$)[76]. Modelling the effect of reallocating just 30 minutes of sitting time to light-intensity physical activity suggests a potential 2–4% improvement in major cardiovascular risk factors[89]. This improvement is supported by the findings of a meta-analysis of free-living interventions targeting sedentary behaviour reductions alone or in combination with increases in physical activity. Pooled effects showed small but significant beneficial effects of the interventions on body mass (~ −0.6 kg), waist circumference (~ −0.7 cm), percentage of body fat (~ −0.3%), systolic blood pressure (~ −1.1 mmHg), plasma insulin level (~ −1.4 pmol/l) and plasma HDL-cholesterol level (~ 0.04 mmol/l)[90]. The effects observed for sedentary behaviour reduction interventions are generally inferior to those reported after exercise training interventions[91,92].

However, to date, most of the evidence comes from sedentary behaviour reduction interventions conducted in the workplace setting. By comparison, a meta-analysis revealed that workplace physical activity interventions have yielded modest pooled effects on body mass (~−2.6 kg) and waist circumference (~−1.9 cm), whereas reductions in blood pressure and blood lipid and glucose levels were not significant[93].

However, the findings supporting interventions to target sedentary behaviour reductions are from studies with limited representation of individuals with clinical conditions pertinent to cardiovascular health (for example, those with cardiovascular disease or type 2 diabetes mellitus), different racial/ethnic groups and older populations (that is, non-working age adults). Furthermore, as is the case for trials of physical activity interventions, a need exists for studies intervening for ≥12 months and including maintenance evaluations from which to consider sustainability and longer-term effectiveness.

As a consequence of the emerging evidence described above, intriguing possibilities arise for future research and clinical innovation. Technological advances in consumer devices provide particular opportunities. Data from wrist-worn activity trackers now deliver feedback on interruptions to sedentary time and on light-intensity activity and moderate–vigorous-intensity activity. These data can already provide clinical starting points to address reductions in sitting time and increase total physical activity, along with relevant goal setting and objective feedback for the individual. Evidence from randomized trials to determine the feasibility and cardiovascular health benefits of the relevant behavioural changes might provide a future basis for specific clinical recommendations.

## Sitting less and moving more

An increased understanding of the effects of sedentary behaviour and physical activity on cardiovascular outcomes and mortality has augmented the interest in understanding the interaction between these behaviours to optimize behavioural-based strategies designed to reduce the risk of cardiovascular disease[94]. Specifically, the interactions between sedentary behaviour and physical activity on the risk of cardiovascular disease have received intense scrutiny in a series of prospective epidemiological studies[29]; the crucial conclusions relating to this interaction are summarized below[94].

First, physical inactivity and sedentary behaviour are both associated with an increased risk of cardiovascular disease incidence and death. Replacing sedentary behaviour with any intensity of physical activity (that is, movement) will have health benefits, with greater benefits seen when sedentary behaviour is replaced with moderate–vigorous-intensity physical activity. Finally, the effects of sedentary behaviour on the risk of cardiovascular disease are most pronounced in individuals who are physically inactive. Furthermore, high levels of moderate-intensity physical activity can ameliorate the increased risk of cardiovascular disease associated with excessive sedentary behaviour. This benefit was revealed in a meta-analysis that included individual-level data from >1 million participants[95]. Higher levels of self-reported sitting time were associated with increased all-cause mortality across categories of moderate-intensity physical activity. However, this correlation did not exist in the highest category of physical activity (>35.5 MET-hours per week, equivalent to ~60–75 minutes per day of moderate-intensity physical activity) in which the risks of sitting are mitigated[95]. Similarly, amelioration of the excess risk associated with high levels of sitting for cardiovascular death (>8 hours per day) and incident cardiovascular disease (≥10 hours per day) is evident only in individuals with higher physical activity levels (~40 to >60 minutes per day)[95]. Consistently across all the studies to date, the detrimental associations between excessive sitting and adverse cardiovascular outcomes are particularly evident among physically inactive individuals (that is, those not meeting the minimum recommendations of >150 minutes per week of moderate-intensity activity).

Although the joint associations between prolonged sitting, physical inactivity and other health outcomes (for example, cardiovascular events and type 2 diabetes mellitus) are beginning to be elucidated, we can nevertheless consider how the evidence for all-cause mortality can be utilized to create a mortality 'matrix'. This matrix will uniquely combine sitting time and physical activity in a way that has relevance to the application of novel management approaches in clinical practice. Despite the widespread use of prediction matrices for the total risk of cardiovascular disease in clinical practice[96], little attention has been given to similar risk matrix approaches for both of these behaviours; it is now possible to begin doing so through the findings of meta-analyses of studies that have measured both sitting time and physical activity in relation to the risk of death.

A SIT-ACT all-cause death risk matrix can assist clinicians to develop treatment decisions for patients who are living with or at risk of developing cardiovascular disease (FIG. 4). Responses to two separate questions that ascertain daily sitting time and physical activity time are fundamental to the application of this risk prediction model. With the use of relevant hazard ratios for all-cause death[95], the estimates for sitting time and physical activity can be applied to directly compare the percentage of risk increment from the combined sitting and physical activity status against the reference category used in the harmonized meta-analysis[95] (individuals who sat the least (<4 hours per day) and those who had the most physical activity (top quartile equivalent to >60 minutes per day of moderate-intensity activity)). The potential clinical utility of considering the interaction between sitting time and physical activity for risk reduction, particularly in physically inactive patients, is provided in FIG. 5, which also describes how to achieve a reduction from a high-risk to a medium-risk of death[97]. This transition could be achieved through two distinct means. One strategy is to increase physical activity to recommended levels (>150 minutes per week or ~30 minutes per day) without changes to sitting time (that is, sitting time remains at >8 hours per day). Another method is to substantially reduce sitting time (reduce from >8 hours per day to <4 hours per day) without changes in physical activity. A further risk reduction

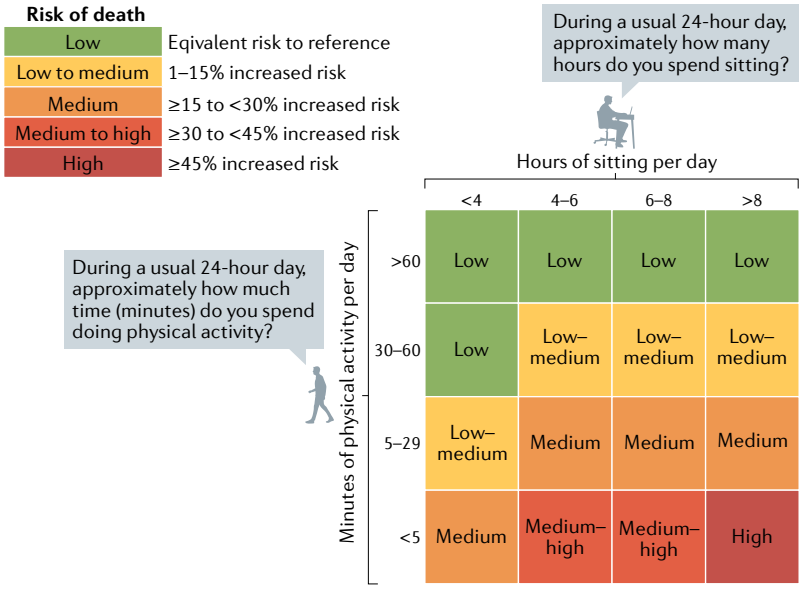


Fig. 4 | **The SIT-ACT risk matrix.** Representation of the SIT-ACT risk matrix[95] showing the interacting influences of sedentary behaviour and physical activity (physical activity includes walking and moderate–vigorous intensity activities) on all-cause mortality. The highest risk of death is evident in individuals who sit the longest and do the least amount of physical activity. Opportunities for risk reduction include both increases in physical activity (to >5 minutes per day), reductions in time spent sitting (to <8 hours per day) or the combination of both increases in physical activity and reductions in sitting time (for example, transition to low–medium risk by increasing physical activity to >5 minutes per day and decreasing sitting time to <4 hours per day). Based on data from REF.[95].

(that is, from high risk to low–medium risk) could be achieved through the combination of an increase in physical activity to recommended levels and a substantial reduction in sitting time (to <4 hours per day).

However, the available evidence that can currently be used to populate the SIT-ACT matrix is from all-cause death findings. Therefore, extrapolations to more specific outcomes, such as cardiovascular disease events or type 2 diabetes mellitus, require caution. Nevertheless, the SIT-ACT matrix provides a framework to consider how different combinations of time spent being physically active and time spent sitting might determine particular health risks. As evidence from large-scale epidemiological studies with cardiovascular disease and other specific health outcomes becomes available, it will be possible to use this framework with a greater degree of specificity with a more disease-specific focus.

## Implications for clinical practice

Although regular, structured physical activity (exercise) effectively reduces cardiovascular risk and improves relevant outcomes, adherence to exercise, even within structured cardiac rehabilitation programmes, can be suboptimal[98]. Furthermore, sitting-induced 'exercise resistance' (as described above) might attenuate the benefits of exercise among those performing suboptimal levels throughout the day. Multimorbidity is pervasive among individuals with cardiovascular disease risk factors and negatively affects health outcomes and mortality, thereby complicating treatment strategies[99,100]. Given the physical complications and pain often associated with multimorbidity, particularly in patients with angina or arthritis[101], the reduction in sedentary time could be a feasible starting point to improve cardiovascular risk factors in these individuals. Given that physically inactive individuals are at a greater total risk of acute cardiac events than physically active counterparts[102], the American College of Sports Medicine recommends light–moderate-intensity exercise in the first instance, especially for individuals who are habitually inactive[103]. Specifically, among inactive adults, reducing sedentary time and thereby increasing light-intensity activity might provide sufficient stimulus and progressive overload that lead to worthwhile improvements in cardiorespiratory and musculoskeletal function[24].

A 'staircase' approach can be applied that focuses initially on reducing and interrupting sitting time (FIG. 5). This approach initially increases standing and stepping time, progressing to increasing light-intensity physical activity volumes and then to increasing moderate–vigorous-intensity physical activity. The staircase approach contrasts with the salutary but formidable primary goal of transitioning from a chronic inactive state to regular engagement in moderate–vigorous-intensity activity and improved cardiorespiratory fitness. In many patients with cardiovascular disease, this approach might seem unrealistic and includes practical challenges and risks, especially for older adults (≥65 years) and those with multiple morbidities. Nevertheless, for individuals who are young (≤45 years) and have an athletic or fitness-training history or who might otherwise be so inclined, starting with increasing moderate–vigorous activity and cardiorespiratory fitness could be appropriate and most beneficial.

Although the conclusions of the meta-analysis described above suggest that total sitting time should be limited to 4 hours per day for individuals who are inactive[95], this goal is likely to be too ambitious for most patients who have a compromised cardiovascular health. Consequently, the optimal prescription should build on the interaction between sitting time and physical activity. This combined approach is particularly relevant in light of findings on sitting-induced 'exercise resistance' because focusing on physical activity alone might not lead to the desired outcomes.

A first step towards integrating more movement into patients' daily lives could include goals of reducing total sitting time by 30 minutes per day or interrupting prolonged bouts of sitting throughout the day. This approach can enable a simultaneous reduction in sitting time and an increase in total physical activity. Although initial interruptions in sitting time might be limited to standing or light-intensity activities, this added movement could increase functional capacity or physical conditioning, thereby preparing individuals for higher intensities of physical activity. An older adult with cardiovascular disease might, for example, be able to increase their leg strength by simply adding several sit-to-stand transitions throughout their day. This added movement might increase their capacity for more physical activity such as walking the stairs. Indeed, several individual-specific and disease-specific factors should be considered when

Total sitting time
Time in which a specific measure of sitting can be derived from a thigh-worn monitor device (for example, the activPAL device), which uses accelerometer-derived information about both thigh position and acceleration to determine body posture (that is, sitting, lying or upright).

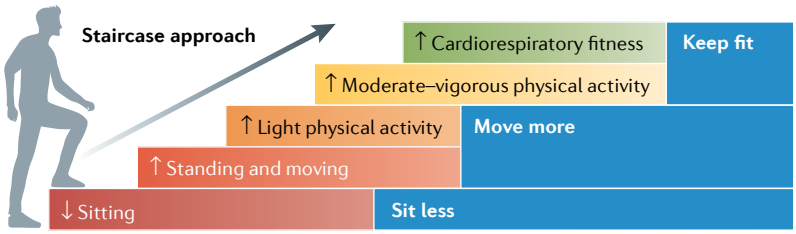


Fig. 5 | **The 'sitting less and moving more' strategy.** Sitting less and moving more might be addressed in clinical practice through a 'staircase approach'. This approach involves modest transitional steps, beginning with a focus on reducing overall sitting time through initially increasing standing and moving and then progressing to increasing light-intensity physical activity. Progressive increases in movement through sitting less and moving more can provide a 'preparation base' for transitioning to higher-intensity physical activities over the longer term. The first step could be a small but manageable step focused on interrupting sitting time with light-intensity physical activity before taking the larger step of incorporating more light-intensity physical activity throughout the day.

providing advice to patients with cardiovascular disease. However, the message to sit less and move more might be more effective at integrating more movement into the day of an individual than a primary focus of accumulating at least 150 minutes per week of exercise. A focus on sitting time reduction has considerable potential for clinical settings in which some patients with cardiovascular disease are likely to require supervised sessions to engage safely in moderate–vigorous-intensity physical activity. Focusing on reducing sitting time (FIG. 5) might be an important first step in making sustainable changes to movement patterns that will support a higher level of overall physical activity for the benefit of cardiovascular health[94].

## Conclusions

Prolonged, uninterrupted periods of sitting contribute to the risk of cardiovascular disease. Time spent sitting also reduces the total physically active time, resulting in diminished overall skeletal muscle activity and leading to detrimental effects on cardiorespiratory fitness and multiple metabolic processes related to cardiovascular health. Observational evidence shows interactions between sitting time, physical inactivity, and all-cause and cardiovascular death. High volumes of sitting can be particularly harmful in individuals who are also physically inactive. In this context, active interruptions to sedentary time have an important role, with evidence from laboratory studies showing beneficial glycaemic, vascular and other changes consistent with lower cardiovascular risk. The findings from real-world intervention trials show that changing sedentary behaviours can be feasible and acceptable and that modest improvements in cardiovascular risk factors can be achieved. However, this evidence is fairly new and requires further confirmatory findings. Taken on balance, both the epidemiological and experimental evidence suggest that less sitting will lead to a cardiovascular health benefit. In clinical practice, a combined approach emphasizing sitting less and moving more could amplify the transition to more physically active lifestyles with cardiovascular health benefits. In this Review, we have considered the current strengths and limitations of the available evidence, highlighting some of the emerging opportunities for further research and suggesting initial implications for clinical practice. The body of evidence needs to be developed and further consolidated to inform future clinical guidelines on sedentary behaviour and cardiovascular health, particularly on dose–response relationships and on appropriate quantitative change targets. However, as we have illustrated in our concluding sections, novel implications arise from the evidence already available, which can help to inform realistic, acceptable and beneficial innovations in clinical practice.

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All the authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article, and undertook review and/or editing of the manuscript before submission.

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