TOPICAL REVIEW

Physical inactivity causes exercise resistance of fat metabolism: harbinger or culprit of disease?

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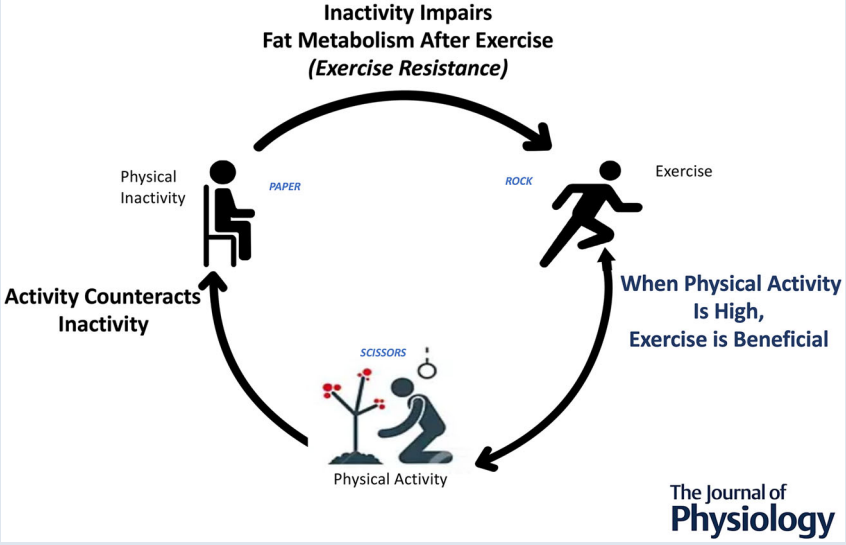

Abstract Physical inactivity is the fourth leading cause of death in the world. It is associated with myriad diseases and premature death. Two possible contributing factors are postprandial lipidaemia (PPL), which accelerates atherosclerosis, and impaired whole-body fat oxidation, which contributes to obesity. Acute exercise in physically active people is effective for increasing whole body fat oxidation and lowering PPL the next morning. However, in people who have low physical activity (<8000 steps/day), an acute bout of exercise (1 h at 62% maximal oxygen consumption) has no effect on increasing fat oxidation or reducing PPL ('exercise resistance'). The acute harms of inactivity are not due to the lack of exercise and are more powerful than the benefits of exercise, at least regarding fat metabolism. The increase in mortality with reduced daily steps is remarkably steep. Low background steps/day also impair the metabolic adaptations to short-term

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endurance training, suggesting that the ills of inactivity extend beyond fat metabolism. 'Exercise resistance' with inactivity could be a culprit, causing atherosclerosis, or maybe also a harbinger (impaired fat oxidation) of more widespread diseases. Recommendations regarding the amount of moderate to vigorous exercise needed for health should factor in the amount of background activity (i.e. ∼8000 steps/day) necessary to avoid 'exercise resistance'.

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Abstract figure legend Prolonged sitting throughout the day with a low step count, as an example of inactivity, impairs postprandial fat metabolism when measured the morning after exercising for 1 h. This is termed 'exercise resistance' because prior exercise normally improves fat metabolism. For optimal fat metabolism and possibly health, exercise is most beneficial when daily physical activity is high because the greater intensity of exercise promotes greater physiological adaptations. Physical activity (defined as >8000 steps/day) is also very important because it counteracts physical inactivity. The ills of physical inactivity are not due to the lack of exercise and appear more powerful than the benefits of exercise. As a result, every 1000 steps/day decrease in physical activity is reported to increase the incidence of cardiovascular disease and death by ∼15%. Physical activity guidelines need to factor in a minimal level of daily background physical activity in addition to exercise recommendations. The interrelationships depicted in this figure are analogous to a popular game rock-paper-scissor.

Introduction

Over the past several decades, automation primarily driven by computer technology has progressively reduced the necessity for physical movement in both work and leisure within modern societies (Bassett et al., 2004). Physical inactivity is the fourth leading cause of death in the world (World Health Organization, 2022). People are spending increasingly more time sitting in front of screens, which is driving the public health crisis that is causing disease in numerous physiological systems (Booth et al., 2012, 2017; Pedersen & Saltin, 2015). However, the physiological mechanisms by which inactivity causes widespread disease are unclear and we are just now gaining insight as to how much and what type of physical activity or exercise is needed to prevent inactivity-associated diseases.

Over the past 75 years, epidemiological studies have been most informative by finding that physical inactivity is highly associated with increased mortality and incidents of cardiovascular disease (Ekelund et al., 2016, 2019; Morris et al., 1953; Paffenbarger et al., 1986; Pedersen & Saltin, 2015). Furthermore, physical inactivity has been associated with dozens of illnesses (Booth et al., 2017; Pedersen & Saltin, 2015). Although the scientific literature contains few hypotheses as to the potential mechanisms by which inactivity produces such widespread disease, one fact is clear: inactivity is not simply the lack of the 'good' from exercise (Bey et al., 2003; Booth et al., 2012, 2017; Hamilton et al., 2008). The acute genetic and molecular responses to exercise are substantially different from the responses to inactivity (Bey et al., 2003; Booth et al., 2017). Exercise and inactivity are two separate and distinct phenomena. This review posits that the ill effects of inactivity on fat metabolism are not counteracted by adding exercise. Each has an independent effect on health, one positive and one negative. As discussed, optimal health may be achieved by maintaining a sufficient level of background activity in addition to performing a sufficient amount and type of exercise. Thus, health recommendations should address not only the role of exercise but also the amount of background physical activity (Hamilton et al., 2008).

Our model

Based upon rodent studies regarding inactivity and lipoprotein lipase activity (Hamilton et al., 2007), our laboratory has focused upon fat metabolism in people as a system that is acutely inhibited by inactivity of only 2 days and maybe less. Our postprandial model (Fig. 1) aims to control physical activity for at least 2–3 days and then have subjects on the evening of the third day exercise for 1 h at ∼ 62% $\dot{V}_{O_2max}$ (maximal oxygen consumption) as this should acutely stimulate fat metabolism the next morning. We further challenge fat metabolism after an overnight fast by giving subjects a high fat meal in the morning of Day 4 (a milkshake also containing fat, carbohydrate and protein) and determine how much this meal increases postprandial fat oxidation as well as plasma triglyceride concentration over a 6 h period (post-prandial lipaemia; PPL) (Fig. 1). If the 1 h bout of exercise fails to improve fat oxidation and lower PPL the next morning, this is a sign of 'exercise resistance', the inhibition of what should be a normal healthy response due to low physical

activity (Fig. 2*B*). This approach has allowed us to describe the amount of background physical activity required to prevent a stalling of postprandial fat metabolism (i.e. low whole body fat oxidation and increased PPL) and to develop practical physical activity recommendations (Burton & Coyle, 2021). It remains to be determined if the presence of exercise resistance might also be a harbinger of the ill effects of inactivity in other bodily systems in addition to fat metabolism.

The pattern with which inactivity stalls postprandial fat metabolism and causes exercise resistance appears similar to the pattern of all-cause mortality with inactivity in terms of increased mortality with decreased steps and parallel increases in PPL and reduced fat oxidation (Banach et al., 2023; Burton & Coyle, 2021; Paluch et al., 2022) (Figs 3 and 4). Impaired fat metabolism may be the proverbial 'canary in the mine' and a *harbinger* or indicator to warn that the consequences of inactivity are present and harming bodily systems. Thus, a harbinger foretells using signals that are a warning or an indirect byproduct of disease. Reduced postprandial fat oxidation appears to be a harbinger of metabolic dysregulation. A *culprit* is the direct cause of the disease. Increased mortality with inactivity might be due directly to the culprit of the postprandial elevation of plasma triglycerides, directly causing atherosclerosis (Zilversmit, 1979, 1995). What is harbinger *vs*. culprit remains to be determined. Identifying the mechanisms of impaired fat metabolism after exercise when previously inactive may identify a molecular trigger for more widespread disease in addition to impaired fat oxidation (e.g. harbinger). As a practical aside, we have reported that prolonged standing produces nearly identical responses to prolonged sitting regarding postprandial fat metabolism, indicating that to counteract inactivity requires muscular movement (Crawford et al., 2020).

Plasma triglycerides and acute exercise

Holloszy et al. (1964) were the first to report that an acute bout of exercise lowers fasting basal levels of plasma triglycerides the next morning. More recently, numerous studies have further shown that acute exercise lowers the next morning's PPL during the 4–6 h period after a high fat meal, at least in subjects that assumedly had sufficiently high levels of background physical activity (Freese et al., 2014). Furthermore, this effect of exercise has been shown to be amplified with increases in exercise duration and intensity (Freese et al., 2014; Trombold et al., 2013). However, most of these studies did not report or control for the amount of physical activity (e.g. steps/day) on the days before exercise. Because most of the subjects in these studies were young and physically active, it is likely they were taking a sufficient number of steps/day (i.e. ∼8000) to prevent exercise resistance (Burton & Coyle, 2021; Trombold et al., 2013). Thus, the literature regarding the effects of exercise on PPL seems to not have recognized the negative effects of the previous day's background inactivity (Frayn, 1998; Freese et al., 2014).

Inactivity is not simply the lack of exercise

Kim et al. (2016) may have been the first to report that inactivity, as judged by a low daily step count, despite being followed by a 1 h bout of exercise elicits low fat oxidation and a very high PPL the morning after exercise (i.e. exercise resistance) (Fig. 2*A*). This is an example

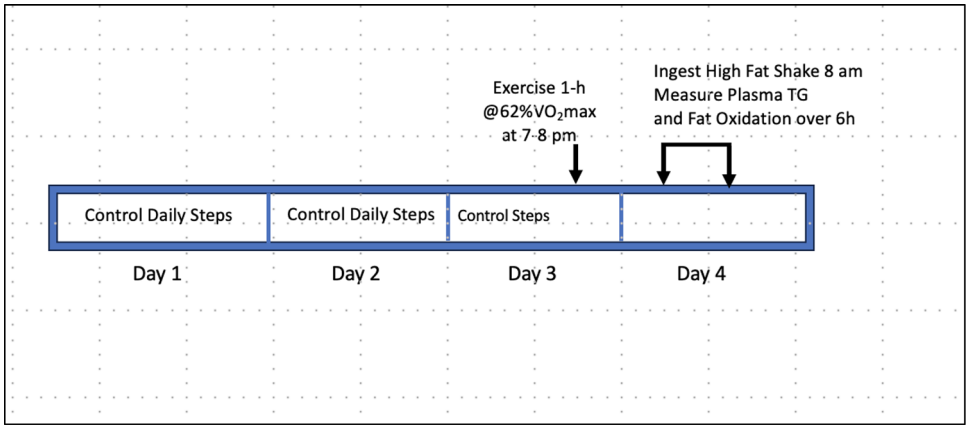

Figure 1. Experimental model used to detect 'exercise resistance'
The goal is to stimulate and then measure fat metabolism (i.e. post-prandial plasma triglyceride elevation and fat oxidation) after ingesting a high fat meal on the morning of Day 4. Fat metabolism was further potentially stimulated by 1 h of exercise performed in the evening of Day 3 (12 h before the high fat meal). The experimental conditions that were varied on Days 1, 2 and 3, were steps/day. 'Exercise resistance' was displayed when the number of background steps/day failed to elicit an improvement in postprandial fat metabolism on Day 4, despite the 1 h bout of exercise on the evening of Day 3.

of why it is wrong to think that inactivity is simply the lack of exercise (Hamilton et al., 2008). In subjects who have been inactive (i.e. low background steps/day), we have also shown that the addition of a 1 h bout of running does nothing to improve fat metabolism, with PPL and fat oxidation being identical to when no exercise is performed (Fig. 2*B*) (Akins et al., 2019). When step count is low, there is exercise resistance compared to both a high step count (Fig. 2*A*) and even when adding 1 h of exercise (Fig. 2*B*). It seems that the unhealthy effects of prior inactivity are more powerful than the normally stimulating effects of exercise, at least regarding fat oxidation and PPL. If inactivity and exercise were responding to the same phenomena, then the effects of inactivity should be countered with exercise. This does not happen (Akins et al., 2019) (Fig. 2*B*). Once inactivity induced exercise resistance sets in, we do not know how long it lasts or what types of activity/exercise or lengths of time are needed to overcome it. Keep in mind that a 1 h bout of exercise at 62% $\dot{V}_{O_2max}$ is ineffective, despite being a moderate intensity of long duration.

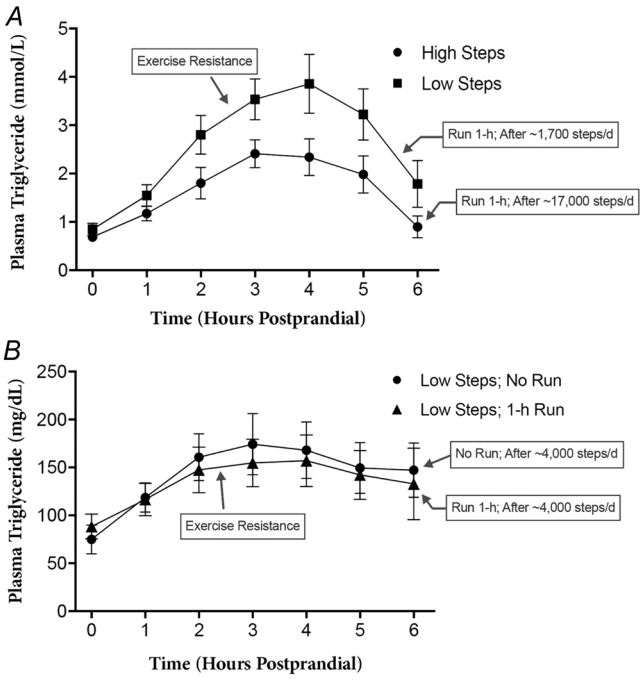

Figure 2. Plasma triglyceride response during the 6-h postprandial period
A, plasma triglyceride response during the 6-h postprandial period when both groups of subjects ran for 1 h the evening after taking either ∼1700 steps/day (low steps) or ∼17,000 steps/day (high steps) the days before. The 1-h run was effective in lowering the postprandial plasma triglyceride response when steps were high but not when steps were low (i.e. 'exercise resistance') (Kim et al., 2016). *B*, plasma triglyceride response during the 6-h postprandial period when the steps were low (∼4000 steps/day) in both trials. Thereafter, in one trial the subjects exercised for 1 h and in the other trial they did not exercise. The 1 h run failed to lower the postprandial plasma triglyceride response (i.e. failed to prevent 'exercise resistance') (Akins et al., 2019). Reprinted and modified with permission from the American Physiological Society.

It has been observed that people who meet the daily recommendations for exercise but who are inactive most of the time outside of exercise are still at higher mortality risk (Biswas et al., 2015; Ekelund et al., 2020; Patel et al., 2010). This is analogous to our experimental model (Fig. 1) whereby sedentary inactive subjects having low background activity (<5000 steps) then run for 1 h (∼10,000 steps) late in the day and are still found to have low fat oxidation and high PPL the next morning. The background inactivity in these people, who have been termed 'active couch-potatoes', causes not only exercise resistance and impaired fat metabolism but possibly augmented development of atherosclerosis (Zilversmit, 1979, 1995). As discussed below, inactivity greatly impairs muscle metabolism. Recently, the effects of inactivity have been extended to brain health by observing that daily sitting of progressively longer than 10 h/day results in increased incidence of dementia in a population averaging 67 years (Raichlen et al., 2023). Like fat metabolism, the effects of inactivity on dementia are not countered by exercise (Raichlen et al., 2023). In both the muscle and the brain, the unhealthy effects of inactivity seem more powerful than the suppressed effects of exercise that are normally beneficial. The observation that muscle and brain appear to be impaired progressively with inactivity and without rescue via exercise suggests inactivity might produce agents that target multiple organ systems. This suggests that recommendations regarding exercise/activity for overall health should minimize sitting and inactivity lengths while also including a minimal level of background activity (e.g. ∼8000 steps/day).

Epidemiological studies are somewhat consistent with each other

One goal is to reconcile epidemiological data describing the pattern with which reducing daily steps increases mortality with our acute observations describing the pattern by which postprandial fat metabolism is impaired by reducing daily step counts. We also determined if background inactivity interferes with adaptations to short term training. Since the pioneering studies of Morris et al. (1953), numerous epidemiological studies have shown that physical inactivity results in a higher risk of heart disease and or all-cause mortality and that inactivity is displayed in most of the population (Banach et al., 2023; Ekelund et al., 2016, 2019; Patel et al., 2010). Studies have varied their measurement tools of physical activity assessment, with step count being our model. A recent meta-analysis by Paluch et al. (2022) showed that taking fewer than ∼8000 steps/day (i.e.

7000 to 9000 steps/day) resulted in a precipitous increase in mortality (Fig. 3*B*). In agreement with this, Lee et al. (2012, 2019) reported that 7500 steps per day was sufficient to almost plateau the risk of all-cause mortality and some studies have generally agreed with this observation (Manas et al., 2022; Tudor-Locke et al., 2011). However, another recent meta-analysis does not see a clear plateau with increasing steps above 8000 steps/day, yet the slope is shallow (Fig. 3*A*) (Banach et al., 2023). Regardless, the most striking feature of both Fig. 3*A* and Fig. 3*B* is the precipitous increase in mortality when steps/day drop below ∼8000 steps/day. Both Fig. 3*A* and Fig. 3*B* (Banach et al., 2023; Paluch et al., 2022) show that each 1000 steps/day (equivalent to walking ∼0.8 km in ∼10–12 min) reduction in background activity below ∼8000 steps/day, is associated with at least an ∼15% increase in mortality risk and risk of cardiovascular disease. The steepness of that relationship

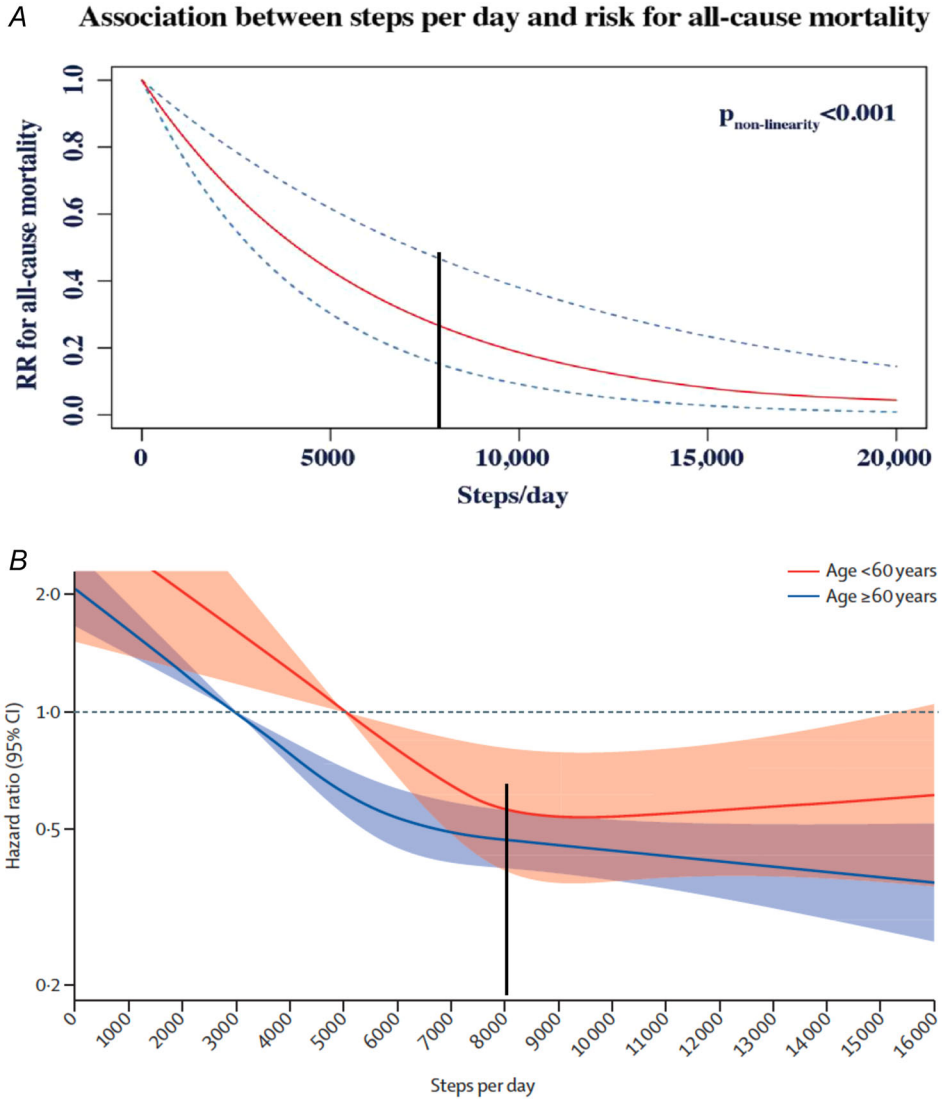

Figure 3. Association of steps/day and risk of all-cause mortality
A, recent meta-analysis (n = 226,889) on the relative risk of all-cause mortality *vs.* steps per day (Banach et al., 2023). The vertical line indicates a comparatively low relative risk at ∼8000 steps/day which is the calculated inflection point of this curvilinear relationship. There is a steep increase in relative risk when steps are reduced below ∼8000 steps/day. *B*, recent meta-analysis (n = 47,471) of Paluch et al. (2022) on the hazard ratio *vs.* steps/day by age group. The vertical line indicates a relatively low hazard ratios at ∼8000 steps per day, the activity level that is recommended by the author for the population in general. In both *A* and *B*, note the precipitous increase in hazard ratio and relative risk when steps/day decrease below ∼8000 steps/day, although this is less obvious in *A*. In both *A* and *B*, the incidence of mortality increased ∼15% with every 1000 step/day reduction below 8000 steps/day. Another reason for selecting ∼8000 steps/day is the fact that exercise resistance can be prevented by taking 8481 steps/day and probably less (Fig. 4). Reprinted and modified with permission.

is remarkable and cannot be overemphasized. It is obvious that low-activity people (<8000 steps/day) can derive huge benefits from even small amounts of added activity. This point is sometimes lost in the 'at least' recommendations of the physical activity guidelines that encourage people to perform 'at least' 150 min per week of moderate intensity exercise or 75 min per week of higher intensity exercise with an additional 2 days per week of resistance training (Piercy et al., 2018). Our data suggest that there should be two areas of recommendation, one for preventing exercise resistance and another for obtaining sufficient exercise. Interestingly, societies that use additional walking or bicycling as a form of transportation experience fewer cases of metabolic syndrome and have better overall health (Guthold et al., 2018; Pedersen & Saltin, 2015). A person getting only 4000 steps/day of background activity will increase their steps/day to 8000 by walking an extra 3.2 km (2 miles) in 30–40 min. That seems broadly achievable, especially when integrated into transportation.

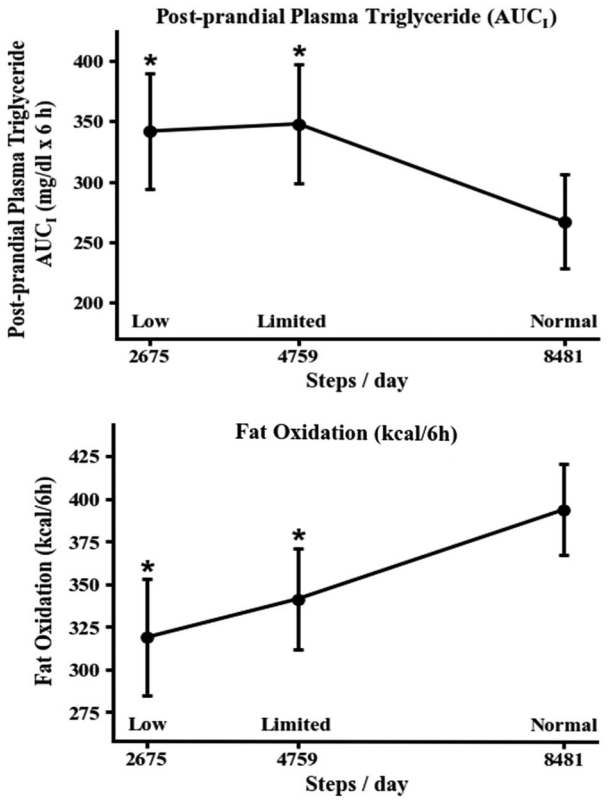

Figure 4. Relationship between the three levels of physical activity in steps/day on the next day's fat metabolism measured during a measure of postprandial plasma triglyceride concentration area under the curve incremental (AUCi) (*A*) and fat oxidation over 6 h (*B*)
The 'Normal' responses when taking 8481 steps/day the day before was a high rate of fat oxidation and a low level of plasma triglyceride concentration during the postprandial test. On the contrary, when taking either Low (2675 steps/day) or Limited (4759 steps/day) exercise, the postprandial triglyceride was significantly elevated (*A*) and fat oxidation significantly reduced (*B*) compared to Normal ($P < 0.05$). *Low and Limited are significantly different from Normal ($P < 0.05$). From Burton & Coyle (2021); reproduced with permission.

Fat metabolism and step count

In order to determine if inactivity caused a similar pattern of harm with fat metabolism as it does with mortality (Banach et al., 2023; Paluch et al., 2022), we had participants vary their baseline step counts over the days preceding the 1 h bout of exercise stimulus followed by the next morning's measures of PPL and fat oxidation (Burton & Coyle, 2021). They took either approximately 2500 or 5000 or 8500 steps/day. The low and medium step counts were not effective at promoting a healthy PPL response or a healthy fat oxidation (Fig. 4). However, taking ∼8500 steps/day was significantly better than both other measures (Burton & Coyle, 2021). This agrees with the epidemiological studies of (Banach et al. (2023) and Paluch et al. (2022) reporting reduced mortality when taking 8000 steps/day compared to <5000 steps/day (Fig. 3). The fact that taking 8481 steps/day was effective in preventing exercise resistance is another reason to recommend 8000 steps/day as a general guideline for preventing 'exercise-resistant inactivity'. Thus, step counts below 8000 steps/day might be considered as being inactive although we currently have no fat metabolism data in the range of 5000 to 8000 steps/day to make a more precise estimate. Classification as 'sedentary' might be based on sitting time and require appropriate metrics. This general agreement between the epidemiological and physiological exercise resistance data raises the possibility that the precipitous increase in mortality and various diseases (Banach et al., 2023; Sheng et al., 2021) when step count is reduced below ∼8000 steps/day may be due to similar mechanisms as the inactivity-induced stalling of fat metabolism, also termed 'metabolic inflexibility' (Chacon et al., 2012). This is not to say it can be concluded that increased mortality with inactivity is due entirely to stalled fat metabolism, although it may be a strong contributing factor (culprit) or just the harbinger of more widespread disease.

Practical application

The steepness of daily steps *vs.* mortality is absolutely remarkable in both models (epidemiology and fat metabolism) (Figs 3 and 4). In sedentary low step individuals, increases in activity of only 1000 steps/day, which amounts to only ∼0.8 km/day of walking, elicit linear reductions in mortality by ∼15% and hazard ratio ∼20%, which are in parallel with improvements in fat oxidation (Figs 3*A*, *B* and 4*B*) (Banach et al., 2023; Burton

Table 1. Percentage changes from pre-training to post-training as a result of short-term training (5 bouts in 9 days) in low-step and high-step groups

	Low step (~4800 steps/day)	High step (~16,000 steps/day)
Plasma triglyceride AUC; high fat tolerance test	−4.2% NS	−27%*
Resting fat oxidation	+6.0% NS	+19%*
Peak oxygen consumption	+7.2%*	+7.6%*
Responses during submaximal exercise at 79% $\dot{V}_{O_2peak}$		
Heart rate	−2.7% NS	−6.6%*
Blood lactate concentration	0% NS	−11.8%*
Deoxy-haemoglobin	+4.7% NS	−7.4%*
Rating of perceived exertion	−7.6% ($P = 0.07$)	−12.2%*

*Significant improvement from pre- to post-training ($P < 0.05$). NS, non-significant. AUC, area under the curve. Reproduced from Burton et al. (2021) with permission.

& Coyle, 2021; Paluch et al., 2022; Sheng et al., 2021). Adding back even moderate amounts of physical activity and ideally raising step count to ~8000 steps/day is a most effective form of preventive medicine with further benefits derived thereafter from additional exercise that is not hampered by exercise resistance. As we have shown, 1 h of exercise against a background of only 4000 steps/day is not going to improve acute fat metabolism or allow chronic metabolic adaptations to short-term training, but taking ~8000 steps/day will allow improvements to be manifested (Burton & Coyle, 2021; Burton et al., 2021). This supports our general recommendation that people should aim to take >8000 steps/day just to prevent exercise resistance and thereafter perform exercise that elevates heart rate and breathing frequency (Piercy & Troiano, 2018). Finally, the impairment of fat oxidation with exercise resistance amounts to 6 g over 6 h which projects to 18 g over a day with three meals, which if accrued over a year's time amounts to a 6.6 kg gain in body fat. That is enough to account for the average gain in body fat within the US population (Parikh et al., 2007).

Effects of inactivity on short-term exercise training responses

The level of background steps/day also influences the adaptations to short-term endurance training. Subjects taking a high number of background steps (16,048 per day) during five training bouts (40 min cycling at 80–90% $\dot{V}_{O_2max}$) over 9 days showed the classic physiological improvements during constant intensity cycling post-training with significantly lower blood lactate, heart rate and perceived exertion with improved muscle oxygenation (Burton et al., 2021) (Table 1). However, in the subjects taking low step count (4767 per day), none of these metabolic measures showed significant improvements. However, both groups displayed a 7% increase in maximal oxygen consumption ($\dot{V}_{O_2max}$) (Burton et al., 2021). This suggests that the metabolic systems involved in fat metabolism, lactate production and heart rate regulation were unresponsive to training in the low step group. However, since $\dot{V}_{O_2max}$ increased equally in the two groups, it might be that central cardiovascular adaptations such as stroke volume and blood volume improved equally (Satiroglu et al., 2021). This 'metabolic exercise resistance' to short term training suggests that the effects of background inactivity extend beyond effects on fat metabolism and may have widespread effects on muscle metabolism with possibly attenuated health adaptations in other systems such as the brain and dementia (Livingston et al., 2020). Our observations show that inactivity impairs fat metabolism after 1 or 2 days or less of reduced activity. It has been claimed that inactivity contributes to dozens of chronic diseases (Booth et al., 2017). It is important to determine which diseases stem largely as a result of the last few days of inactivity such as insulin resistance, as opposed to diseases that progress over longer times such as atherosclerosis (Heath et al., 1983; Zilversmit, 1995). Since low background activity blunts general metabolic adaptations to exercise training, this would be a source of individual variability with apparent 'non-responders' to training when background activity is not sufficiently high as is typically the case with Type II diabetics (Sparks, 2017). Clearly, exercise resistance has influences beyond short term fat metabolism.

Prolonged low intensity exercise and sprints with high intensity interval training

We have shown that inactivity stalls resting fat oxidation, yet it is possible to prevent that by taking 8500 steps/day

at low to moderate intensity throughout the day. Furthermore, Hamilton et al. (2022) have argued that frequent isolated soleus muscle contractions, performed while seated, can improve postprandial glucose metabolism, total plasma triglycerides and very low density lipoprotein concentrations over several hours. Thus, both forms of mild exercise frequently performed periodically over prolonged periods seems to prevent metabolic stalling of both fat and glucose metabolism. Additionally, fat oxidation and PPL can also remain at healthy levels despite prolonged sitting, by vigorous inertial load cycling done hourly throughout the day that totals only 2–3 min/day of actual exercise (Wolfe et al., 2020). After control days with somewhat low background steps, participants performed 20 s of intense cycling every hour for 8 h, broken into 4-s sprints and rest, performed 5 times. The next morning, the group that performed the sprints displayed significantly higher fat oxidation and lower PPL despite prolonged sitting (Fig. 5) (Wolfe et al., 2020).

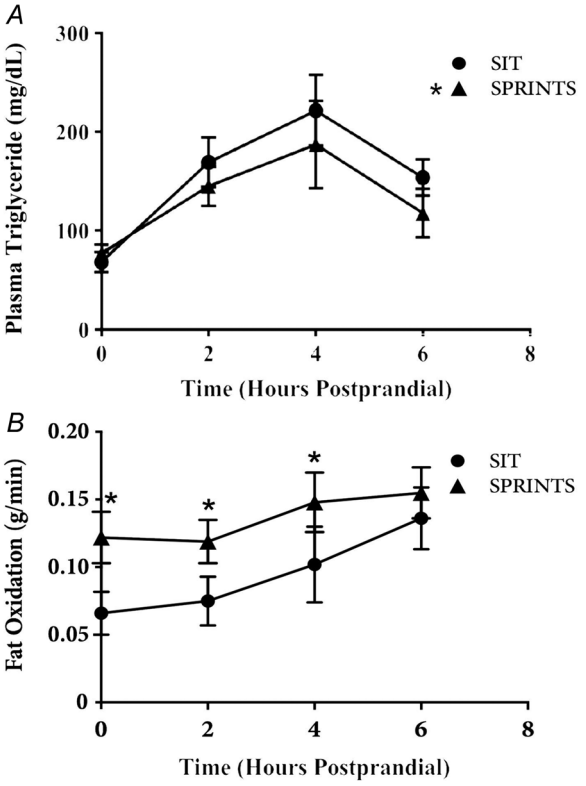

Figure 5. Plasma triglyceride concentration during the 6 h period after ingesting a high fat meal the morning after subjects, on the previous day, either sat continuously for 8-h (SIT) or also sat for 8-h but interrupted the sitting every hour with seated cycling SPRINTS of only 4-s duration performed 5 times with 'all-out' effort
A, the SPRINT trial elicited a 31% reduction in the AUC of plasma triglycerides compared to SIT (* $P < 0.01$). *B*, the SPRINT trial elicited a 43% elevation in fat oxidation compared to SIT (* $P < 0.01$). (Wolfe et al., 2020). Reproduced with permission.

The emerging picture is that sufficient movement is healthy and that the more vigorous the activity the more time-efficient its effectiveness (Gillen et al., 2016), probably by recruiting more muscle mass, especially the Type II fibres (Chi et al., 1983; Hamilton et al., 1998, 2007; Skelly et al., 2021). High intensity interval training (HIIT) is remarkably effective for raising mitochondrial activity and probably fat oxidation especially in Type II muscle fibres (Boullosa et al., 2022; Kristensen et al., 2015). The common feature of models using soleus contractions, or walking or 4-s repeated sprints is that muscle contractions were performed at least every hour suggesting that some aspect of muscle contractions and frequency are needed to prevent exercise resistance and that only 5000 steps/day does not deliver that stimulus (Burton & Coyle, 2021; Hamilton et al., 2022; Wolfe et al., 2020).

Recently, a possible role for small amounts of vigorous movements throughout the day have been associated with reduced mortality (Stamatakis & Ahmadi, 2022). It is reported that benefits can be gained with as little as 15–20 min/week of vigorous movement (Stamatakis et al., 2019). There has also been interest in the benefits to glucose metabolism of performing short bouts of somewhat vigorous activities throughout the day (e.g. climbing stairs, fast walking, etc.) (Islam et al., 2022). Maybe the goal in breaking up sedentary time is to simply not allow enough 'inactive time' to pass which causes a phenomenon like exercise resistance.

Other models of inactivity

Other models of inactivity, besides reduced step count include the extreme measures of limb immobilization or prolonged bed rest with a focus typically on carbohydrate and protein metabolism. In keeping with our model of inactivity through reducing daily steps, a reduction from ∼10,000 to 1500 steps/day reduced glucose uptake during a hyperinsulinaemic–euglycaemic clamp when first measured after 2 weeks while also impairing post-prandial muscle protein synthesis, muscle mass and insulin sensitivity (Alldritt et al., 2021; Breen et al., 2013). One week of bed rest produces muscle insulin resistance (Dirks et al., 2016). In work from Paul Greenhaff's lab using bed rest and a hyperinsulinaemic–euglycaemic clamp, glucose disposal is reduced as much after 3 days as after 56 days (Shur et al., 2022). Using forearm immobilization, they also reported that postprandial glucose uptake is reduced as much after 24 h as after 72 h (Burns et al., 2021). Furthermore, an early study (Heath et al., 1983) measured insulin sensitivity during an oral glucose tolerance test after chronic exercise training the day before and after 10 days of inactivity and then again after 1 day of retraining. The large declines in insulin

sensitivity with inactivity were almost totally reversed with only 1 day of exercise. The general picture seems to be that postprandial fat, carbohydrate and possibly protein metabolism can be blunted with as little as 1–2 days of no exercise. Insulin sensitivity can be restored with 1–2 days of exercise. We do not know if 1–2 days of activity (e.g. >8000 steps/day) can restore fat metabolism after inactivity induced exercise resistance. The time course of reduced fat metabolism with inactivity and restoration may be short (Bey & Hamilton, 2003), especially if fat metabolism follows lipoprotein lipase activity, which has a time course of only 4–8 h (Seip et al., 1995, 1997). This suggests that many of the metabolic changes with exercise or inactivity happen quickly and probably are largely influenced by the physical activity over the past day or last training bout. Time periods of inactivity lasting 4–23 h have not been reported, raising the possibility that some of the effects of inactivity on impairing metabolism may set in over a remarkably short period and may require very frequent activity/exercise to prevent. Although we have not found a small amount of extra carbohydrate after exercise alters postprandial lipid metabolism, it seems that a large amount can influence it (Harrison et al., 2009; Kim et al., 2016)

Summary

Mortality increases dramatically as background physical activity levels decrease below ∼8000 steps/day, which also induces a stalling of fat metabolism (reduced fat oxidation and increased postprandial lipaemia). This may be atherogenic and possibly make inactivity the main *culprit* of increased mortality with inactivity. The stalling of postprandial fat metabolism can be prevented by taking ∼8500 steps/day. When the effects of inactivity have set in (i.e. 'exercise resistance'), not even a 1 h bout of exercise can reverse it, indicating that the ills of inactivity are not simply the absence of exercise: it is a powerful and an independent risk factor in health. This agrees with the observations that people who meet the recommended level of exercise are still at increased risk of mortality if they are largely inactive throughout the day. Furthermore, chronic short-term exercise training with a low amount of background steps will also inhibit some metabolic adaptations suggesting that inactivity might have widespread harm beyond fat metabolism which could make 'exercise resistance of fat metabolism' a *harbinger* of more widespread disease. In agreement, inactivity has been shown to impair insulin sensitivity and thus also carbohydrate metabolism after only 24 h. Besides increasing steps, the effects of inactivity can be negated through hourly brief (4 s × 5) high intensity cycling, suggesting that more time efficient methods besides increasing steps can also prevent 'exercise resistance'.

It seems that today's modern societies might have passed a proverbial tipping point in that the average daily step count of the populations (e.g. ∼5000) (USA: 4774; UK: 5444) (Tison et al., 2022) is less than that needed to maintain health in general and fat metabolism specifically (e.g. ∼8000 steps/day). It is hoped that this knowledge can be used to factor in the needed amount of background activity to complement any guidelines for moderate to vigorous exercise in order to avoid exercise resistance. Both factors of exercise prescription and sufficient background activity are needed to derive the full health and performance benefits of physical activity and exercise training.

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Additional information

Competing interests

As a matter of Financial Interests Disclosure, the author, E. F. Coyle, owns equity in Sports Texas Nutrition Training and Fitness, Inc., a company that sells the inertial-load ergometer (i.e. sprint) mentioned in this review. The results are presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation.

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Sole Author.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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