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Physiology of physical inactivity, sedentary behaviors and non-exercise activity: Insights from space bedrest model

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Abstract

Physical inactivity, i.e., not reaching the recommended level of physical activity (PA) and sedentary behaviors (SB), i.e., sitting time have been associated with increased risk for common metabolic diseases. Recent epidemiological data suggest that high volumes of SB are detrimental for metabolic health, even in the presence of regular exercise, i.e., moderate/vigorous (MVPA). This suggests that the health effects of SB are independent from those of exercise. However, experimentally testing this hypothesis is complicated because of the difficulty in disassociating SB from PA. Bedrest studies, a traditional space science model, can offer new insights. In some bedrest studies, an exercise training protocol has been used to counteract the harmful effects of inactivity. While bedrest induces an inactive and sedentary state, exercise with bedrest represents a unique model of sedentary yet physically active people. Here, we review bedrest studies with and without exercise training. Although exercise training prevents the loss of muscle mass and function, even large volumes of exercise are not sufficient to fully counteract the negative metabolic adaptations triggered by inactivity. This observation supports the existence of independent adverse health effects of SB, but also the potential benefits of non-exercise activity, i.e., daily living light-intensity activities (LPA). We gathered available data to examine the complex relationships between exercise, non-exercise activity, SB and health outcomes. Given the large amount of SB in modern societies, the sole promotion of exercise, i.e., MVPA may be insufficient, and promotion of LPA may be a complimentary approach to improve health.

Graphical Abstract

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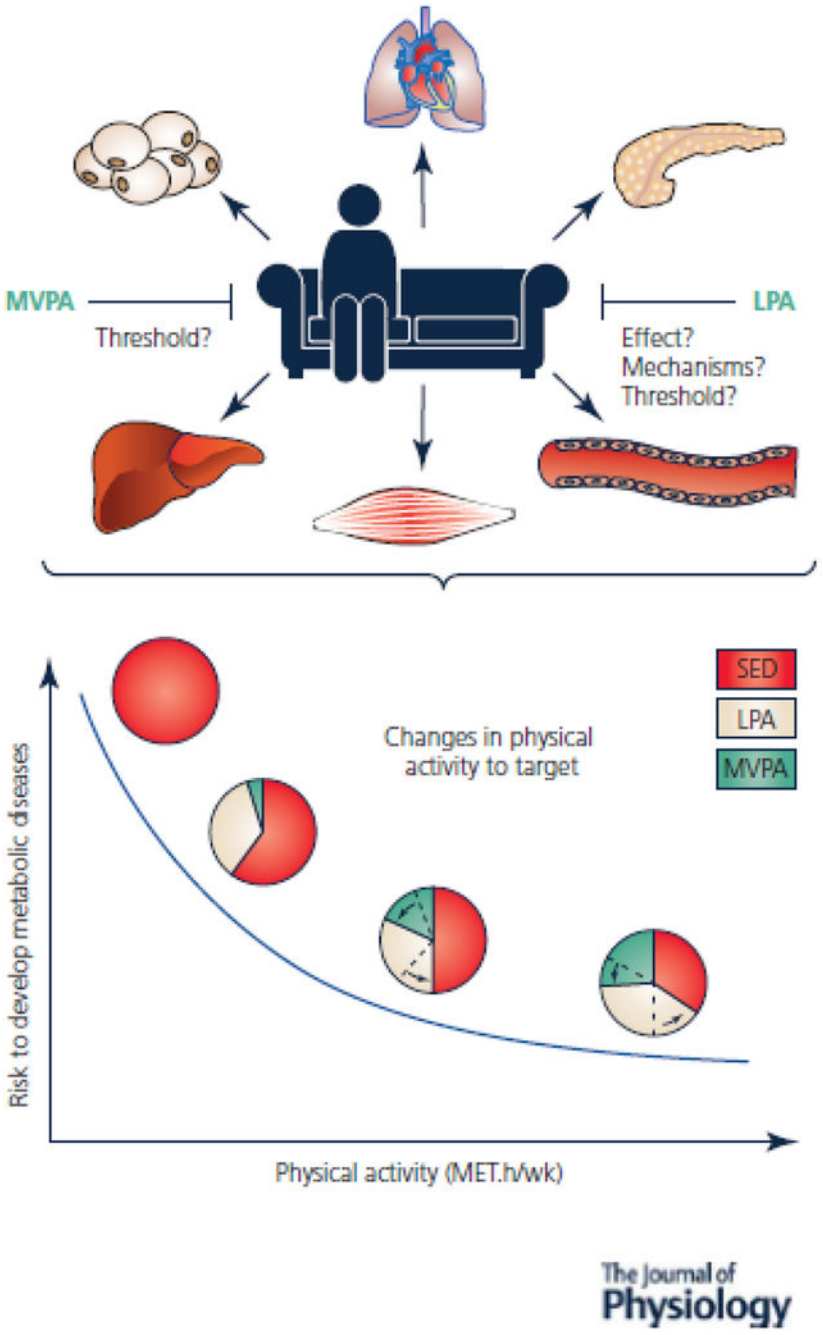
E.L.R., N.D.J. and A.B. wrote the first draft of the review, and all authors contributed to revising and editing the paper. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Conflict of interest

No conflict of interest to declare.



Although the exact physiological mechanisms remain unclear, sedentariness has been shown to negatively affect metabolic health and the main organs involved in its regulation. The 2020 World Health Organization (Bull *et al.*, 2020) guidelines on physical activity recommend practicing a weekly volume of 150–300 min of moderate intensity or 75–150 min of vigorous intensity or an equivalent combination of MVPA to limit the appearance of certain maladaptation. Recently, some large-scale studies have revealed the importance of LPA to prevent the effects of sedentary lifestyles. Since then, limiting periods of sedentary time have become part of the recommendations for the first time, raising the question of how to reduce periods of sedentary living. This review

aims to highlight the potential role of LPA in effectively reducing sitting time and preventing its associated harmful health effects. Intervention studies specifically targeting LPA and SB, in addition to MVPA, are necessary to develop specific recommendations and limit the risk of developing metabolic diseases.

Keywords

Physical inactivity; moderate to vigorous physical activity; light physical activity; bedrest; exercise; non-exercise activity; metabolism

Introduction

Insufficient physical activity (PA) is a public health concern and a major risk factor for early mortality and common chronic diseases including obesity, metabolic syndrome, insulin resistance, type 2 diabetes (T2D), certain type of cancers, mental health disorders and others (Lee *et al.*, 2012). Through research efforts to develop strategies to combat physical inactivity, scientists have identified another health risk behavior: sedentary behaviors (SB). SB are distinct from physical inactivity. Although physical inactivity is defined as engaging in less PA necessary to meet the current guidelines (<150 min/week moderate or <75min/week vigorous physical activity – MVPA, with energy expenditure above 3.0 metabolic equivalent or METs), SB correspond to "any waking behavior characterized by an energy expenditure <1.5 METs, while in a sitting or reclining posture" (Tremblay *et al.*, 2017). Although the recommendations encourage reducing periods of SB, no specific strategy has been proposed to combat the effects of sedentary lifestyles (Bull *et al.*, 2020).

SB are found in every domain of modern daily life: transportation, occupational (e.g., desk bound work) and leisure time activities (e.g., video gaming and internet). Adults in Westernized societies spend between 7.7 and 9.7 h/d sitting, which corresponds up to 60% of adult wake time (Ekelund *et al.*, 2019). Several epidemiological studies have reported associations between sedentary time and health outcomes including early mortality, risk of T2D, metabolic syndrome and cardiovascular disease (Dunstan *et al.*, 2012). These associations were observed in both sexes, all ages, ethnicities and independent of adiposity. They were also found in individuals who reach the recommended levels of MVPA, which suggests that SB is a stand-alone factor in the relationship between PA and health. In other words, spending too much time sitting may have different health effects than not exercising enough. While a plethora of epidemiological data is published, experimental evidence supporting the adverse health effects of SB independent of time spent physically active is lacking. This is mainly due to challenges in isolating the effects of SB from those of PA.

The bedrest model can provide unique insights on the independent health effects of SB. Bedrest studies have traditionally been used by the International Space Agencies to understand the physiological effects of microgravity. During these studies, physically active healthy participants free from any predisposition for chronic diseases stay in bed 24h/7d. They are both physically inactive and highly sedentary (figure 1). In some bedrest studies, the efficacy of exercise training protocols to protect the body against the harmful effects of

microgravity have also been tested. Participants in these studies perform exercise training (figure 1) while in bedrest. Participants in these studies are both sedentary and physically active, and represent an extreme but unique model of “sedentary exercisers”. Another distinctive characteristic of these bedrest exercisers is that they have very low levels of non-exercise activities of daily living, which correspond to light-intensity physical activities (LPA) with an energy expenditure between 1.6 and 2.9 METs (e.g. walking, taking the stairs, standing, etc.) (figure 1).

The objective of this review is to present experimental evidence from bedrest studies with or without concomitant exercise training to provide new information on the metabolic health effects of SB independent from those of MVPA/exercise. To better understand the complex relationship between SB, LPA, MVPA and metabolic health outcomes, we will also review briefly the health benefits of LPA.

The physiology of physical inactivity: insights from strict bedrest investigations

To understand the respective effects of SB and PA, it is important to first briefly summarize the physiological effects of combined sedentariness and physical inactivity induced by strict bedrest (figure 2). Bedrest induces hypokinesia (loss of body movements) and hypodynamia (loss of strength and power), which leads to modifications in all physiological systems (Bergouignan *et al.*, 2011). Among other changes, bedrest reduces muscle function and mass as demonstrated by muscle atrophy and a shift from slow oxidative to fast glycolytic muscle fibers (Trappe *et al.*, 2007a; Salanova *et al.*, 2008; Trappe *et al.*, 2008), reduced mitochondrial volume and oxidative capacity (Kenny *et al.*, 2017), and an impaired expression of genes involved in mitochondrial function (Alibegovic *et al.*, 2010b). Bedrest also rapidly decreases insulin sensitivity in muscle (Alibegovic *et al.*, 2009) in association with lower content and activity of key proteins involved in glucose transport, phosphorylation and storage (Biensø *et al.*, 2012). This results in hyperinsulinemia to maintain normal glucose disposal. This development of glucose intolerance seems to be preceded by a metabolically inflexible state, i.e. an inability of the body to adjust substrate use to changes in substrate availability (Rudwill *et al.*, 2018). Gene expression and activity of enzymes coupled with oxidative metabolism are decreased (Bergouignan *et al.*, 2009; Alibegovic *et al.*, 2010b; Fernandez-Gonzalo *et al.*, 2020) in association with a reduction in lipid oxidation in favor of carbohydrate oxidation (Bergouignan *et al.*, 2006; Bergouignan *et al.*, 2009). These changes are particularly relevant following meal ingestion since they lead to decreased clearance of dietary lipids, which contributes to hyperlipidemia. Despite reduced adipose tissue lipolysis (Alibegovic *et al.*, 2009; Alibegovic *et al.*, 2010a), excess of plasma lipids enhances fat accumulation in the visceral adipose depot (Belavý *et al.*, 2014) and ectopic fat storage in muscle, liver and bone (Bergouignan *et al.*, 2009; Trudel *et al.*, 2009; Trudel *et al.*, 2012; Rudwill *et al.*, 2015). This in turn exacerbates the development of insulin resistance. Fat accumulation in liver likely stimulates *de novo* lipogenesis and an increased synthesis of atherogenic lipid particles (VLDL), as suggested by a recent study in free-living individuals who reduced their PA levels (Damiot *et al.*, 2019). This increased secretion of VLDL further facilitates hyperlipidemia and ectopic fat storage. A decrease

in high-density lipoprotein (HDL) cholesterol, known to be associated with a reduction in cardiometabolic risk, has also been observed (Alibegovic *et al.*, 2009). Concomitantly, the liver is less able to suppress hepatic glucose production, which results in increased gluconeogenesis, thus worsening hyperinsulinemia. These changes are finally associated with the development of low-grade inflammation as indicated by an increase in plasma pro-inflammatory markers (Rudwill *et al.*, 2013; Mutin-Carnino *et al.*, 2014).

All these metabolic features are commonly observed in individuals with obesity, T2D or metabolic syndrome. These observations therefore support a key role of physical inactivity in the onset and progression of metabolic diseases. Although the health enhancing effects of exercise (or MVPA) on these metabolic outcomes are well established, it is unclear whether they are sufficient to reverse the adverse health effects of sedentariness.

Can MVPA reverse the adverse health effects of physical inactivity and SB?: Insights from bedrest studies with concomitant exercise training

To the best of our knowledge, 10 bedrest studies have tested the protective effects of an exercise training program against the metabolic alterations induced by bedrest. These studies span from 20 to 90 days and the exercise prescriptions varied in the type (resistance or aerobic exercise), duration, frequency and intensity (Table 1). Some training protocols were below the current recommendations for PA while others were above. Results have been reported in 26 published articles and are summarized in figure 2.

Effect of resistance exercise alone:

Resistance exercise has been shown to mitigate the decrease in cardiorespiratory fitness (Guinet et al., 2020; Kenny et al., 2020) and prevent the loss of muscle function and mass including the reduction in fiber diameter during bedrest (Trappe et al., 2004; Moriggi et al., 2010). However, the mechanisms underlying the protective effects of resistance exercise against unloading-muscle atrophy are not fully clear. Resistance exercise was shown to prevent the bedrest-induced decrease in muscle protein synthesis (Ferrando et al., 1997) and downregulate the gene expression of myostatin (Irimia et al., 2017), a myokine known to contribute to muscle wasting. The effect of resistance exercise on muscle protein balance, i.e. muscle protein synthesis and breakdown, during bedrest is however still unknown. Despite these positive effects on skeletal muscle, resistance exercise only partially prevents the whole-body metabolic alterations induced by bedrest. It protects against the rise in visfatin (Rudwill et al., 2013), an adipocytokine that mimics the effects of insulin, but does not prevent the increase in IL-6 and C-reactive protein, two pro-inflammatory markers, or the decrease in adiponectin (Brooks et al., 2014), a change associated with inflammation, lipid abnormalities, and insulin resistance. Even when performed at high intensity, resistance exercise does not mitigate the decrease in HDL (Brooks et al., 2014; Guinet et al., 2020), the development of insulin resistance, hyperlipidemia, or the shift towards the use of carbohydrate as fuel (Bergouignan et al., 2006). This later observation is surprising knowing that resistance exercise prevents against the shift of muscle fibers from oxidative to glycolytic types (Trappe *et al.*, 2004), offsets the transcriptomic alterations in muscle related to aerobic energy metabolism (e.g. electron transport chain, fatty acid beta-oxidation

and tricarboxylic cycle pathways) (Fernandez-Gonzalo et al., 2020), and partially maintains the activity and gene expression of enzymes controlling oxidative metabolism (e.g. citrate synthase, succinate dehydrogenase) at the mitochondrial level (Irimia et al., 2017). Although resistance exercise alone does not restore the levels of fatty acid oxidation to baseline values (Bergouignan et al., 2006), no accumulation of fat in bone (Trudel et al., 2012) or visceral depots (Belavý et al., 2014) was reported. Furthermore, no data exists on the effects of resistance exercise on ectopic fat storage in liver or muscle during bedrest. In all these studies, the resistance exercise session was performed as a single continuous bout; however novel data suggest that spreading activity throughout the day as multiple short active bouts may have more potent health-enhancing effects (Loh *et al.*, 2019). Nevertheless, when exercise was performed as intermittent, frequent jumping squats spread throughout the day muscle mass loss was prevented, but not the reduction in whole-body and peripheral insulin sensitivity (Ward *et al.*, 2020). Taken together, the low energy expenditure associated with resistance exercise (Table 1) may be responsible for partial or limited protective effects on metabolic health.

Effect of combined resistance and aerobic exercise:

The majority of bedrest studies has combined aerobic exercise with resistance exercise, which likely induced a greater energy expenditure compared to resistance exercise alone. This training approach preserves or at least attenuates cardiorespiratory fitness, muscle structure and function, leg muscle size and power, muscle strength and endurance, muscle fiber composition and diameter and mitochondrial content and oxidative capacity (Trappe *et al.*, 2007a; Trappe *et al.*, 2007b; Salanova *et al.*, 2008; Trappe *et al.*, 2008; Bergouignan *et al.*, 2009; Krainski *et al.*, 2014; Lee *et al.*, 2014; Ploutz-Snyder *et al.*, 2018). Although muscle alterations were prevented by all the tested resistance and aerobic exercise protocols regardless of the type, duration, intensity and frequency of the training, the protective effects on metabolic outcomes were variable. Combined resistance and aerobic exercise training prevents the development of a pro-inflammatory state (Mutin-Carnino *et al.*, 2014), insulin resistance and the shift in substrate use from total fat oxidation to carbohydrate oxidation (Bergouignan *et al.*, 2009). However, it does not counteract the increase in fasting triglycerides, the reduced oxidative rate of dietary fatty acids likely due to an impaired transport of fatty acids into the myocyte, and fat accumulation in skeletal muscle (Bergouignan *et al.*, 2009) and bone (Trudel *et al.*, 2009). Hepatic fat accumulation is however likely offset (Rudwill *et al.*, 2015). Surprisingly, these alterations were observed despite levels of MVPA mostly above recommended levels (Table 1), and total daily energy expenditure maintained to pre-bedrest levels in the exercising participants (Bergouignan *et al.*, 2010).

Taken together these studies show that exercise (or MVPA) protects skeletal muscle mass and function, and cardiorespiratory function against large volumes of SB induced by bedrest. However, even if a dose-response relationship exists (Figure 2 and Table 1), very high levels of exercise do not fully prevent the manifestation of metabolic dysfunction, i.e. whole-body insulin resistance, glucose intolerance, alterations of lipid metabolism, and systemic inflammation. These observations support the role of organs other than muscle in the health-enhancing effects of physical activity (Thyfault & Bergouignan, 2020), and the

existence of health effects of SB independent of those from MVPA. It further highlights the importance of non-exercise activity (i.e. LPA), which mainly corresponds to daily living activities performed throughout the day.

Health benefits of daily living activities

Evidence from epidemiological studies indicate that LPA has a potential role in reducing the risk of early mortality. In cross-sectional studies, LPA is favorably associated with waist circumference, body mass index (BMI), plasma triglyceride, insulin, HDL-cholesterol concentrations (Amagasa *et al.*, 2018) and 2h plasma glucose (Healy *et al.*, 2007), independent of MVPA. Iso-temporal substitution modelling suggests that replacing 30 min of SB per day with 30 min of LPA (and not MVPA) is associated with lower waist circumference and BMI (Healy *et al.*, 2015). A growing number of experimental studies have also examined the effects of LPA prescribed as short bouts spread throughout the day on metabolic health (table 2). As previously reviewed (Dempsey *et al.*, 2016a), LPA bouts (15–40 min) acutely decrease postprandial glycemia and insulinemia. Even brief intermittent bouts (≤5 min) of walking spread throughout the day reduce glucose and insulin concentrations following meal ingestion, with more potent effects observed in adults with overweight to obesity and T2D (Chastin et al., 2019), and those with lower cardiorespiratory fitness compared to healthy lean individuals (McCarthy et al., 2017). Importantly, acute exposure to bouts of LPA elicits similar responses to those observed with short, frequent bouts of MVPA. With regards to standing, although some studies did not show a reduction in postprandial glycemic response (Bailey & Locke, 2015; Pulsford *et al.*, 2017), others did (Benatti *et al.*, 2017). Benatti and colleagues even reported that intermittent standing, but not a single continuous bout of MVPA, lowers postprandial glycemia in healthy adults. The difference in the observed effects may be explained by the duration of the standing bouts (2 min vs 15 min) and the total active duration (30 min MVPA vs 15 min standing every 30 min for 8.5 hours). Although these acute studies suggest that LPA of higher energy expenditures or longer duration decrease glycemia and insulinemia in a dose-dependent manner, none of these studies controlled for energy expenditure across the interventions. In an elegant series of studies, Duvivier and colleagues compared the metabolic effects of replacing SB with LPA walking and standing to those of 1h/d of MVPA. Both interventions lasted four days and were matched for energy expenditure. Replacing SB with high volumes of LPA without any increase in MVPA, decreased postprandial insulin, fasting triglycerides and non-HDL cholesterol in healthy adults (Duvivier *et al.*, 2013). In adults with T2D, increasing time spent standing and walking improved glucose control and insulin sensitivity. It further reduced diastolic blood pressure, blood triglycerides and non-HDL cholesterol while increasing HDL cholesterol (Duvivier *et al.*, 2017a; Duvivier *et al.*, 2017b). The MVPA intervention tended to improve these metabolic parameters, but the effects were less pronounced. These studies show that when energy expenditure is matched, replacing SB with high volumes of LPA (i.e. non-exercise activity) is more beneficial than performing MVPA as a single continuous bout (i.e. structured exercise), at least for glucose control, insulin sensitivity and circulating lipids. On the contrary, if frequent LPA bouts (>2 min) improves endothelial function (Thosar *et al.*, 2015; Dempsey *et al.*, 2016b), a single bout of MVPA may be more beneficial for microvascular function

than increasing LPA throughout the day (Duvivier *et al.*, 2018). These findings suggest that MVPA (i.e., exercise) and LPA (i.e., non-exercise activity) might elicit differential cardiometabolic effects. Future studies will need to further compare the effects of LPA versus MVPA on cardiometabolic health outcomes, including maximal aerobic capacity, muscle strength, substrate metabolism, glucose control, and insulin sensitivity in different populations and investigate the mechanistic underpinnings.

Where do we go from here?

Although MVPA produces a myriad of health benefits, it does not reduce time spent sedentary. Indeed, physically active people, even those who exceed the current guidelines, can be as sedentary as their inactive counterparts (Rantalainen *et al.*, 2018). Increasing MVPA can even trigger spontaneous behavioral compensations in sedentary adults leading to a decrease in non-exercise activities (i.e. LPA) in favor of sedentary time (Lefai *et al.*, 2017). Furthermore, MVPA does not fully offset the adverse health effects of large volumes of SB, as shown by the bedrest studies with concomitant exercise training. The remaining question is how much MVPA is needed to offset the effects of a certain amount of SB. It was shown that independent of physical activity, every hour spent sitting increases the risk of mortality by 5.9%, of T2D by 22% and of obesity by 23% (Hu et al., 2003; Wilmot et al., 2012; Chau et al., 2013). A meta-analysis including more than 1 million individuals further showed that 60–75 min/d of MVPA are needed to prevent the risk of premature death associated with 9h/d or more of sitting time (Ekelund *et al.*, 2016); 9h/d being close to the average sitting time observed in modern societies. When most of the population does not reach the recommended guidelines (i.e. 30 min/d of MVPA, 5d/wk.), adding 30–45 more minutes per day of MVPA is unrealistic. Therefore, other pragmatic and efficient strategies are needed.

Activities of daily living (i.e. LPA) are inversely associated with SB; increases in LPA are associated with reductions in sedentary time (Pate *et al.*, 2008). In addition, large volumes of LPA, here considered as any body movements associated with activities of daily living, have been shown to confer health benefits. Knowing that lack of time is a major barrier to the practice of exercise/MVPA, reintroducing LPA into daily life could be an effective strategy to reduce sedentary time and prevent its effects on metabolic health. In this line, the latest guidelines from the World Health Organization (Bull *et al.*, 2020) promote the practice of physical activity of any intensity to reduce sedentary activities. In other words, moving is better than sitting. Future mechanistic studies will need to establish the physiology of SB and LPA to better understand the respective negative and positive health effects, and thus better define the dose-response relationship between the components of PA behavior and key health outcomes. Experimental research examining these relationships will foster the development of more specific and pragmatic public health guidelines.

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Biography

The authors are a group of researchers from the University of Colorado in the USA, the French National Centre for Scientific Research (CNRS) and the University of Lyon who are experts in metabolism, exercise and physical inactivity physiology. Elisa Le Roux and Nathan DeJong are graduate students working under the mentorship of Audrey Bergouignan. Stéphane Blanc, PhD, is studying the role of environment on the regulation of energy balance. Chantal Simon, MD, PhD, is professor of Nutrition and expert in metabolism, physical activity and sedentary behaviors. Daniel Bessesen, MD, is an endocrinologist who studies the regulation of body weight at the University of Colorado. Audrey Bergouignan, PhD, is an expert in metabolism, sedentary behaviors and physical inactivity physiology. The group, led by Dr Bergouignan, is building an international lab including members from the two institutions to address the role of sedentary behaviors in the onset and progression of metabolic diseases.

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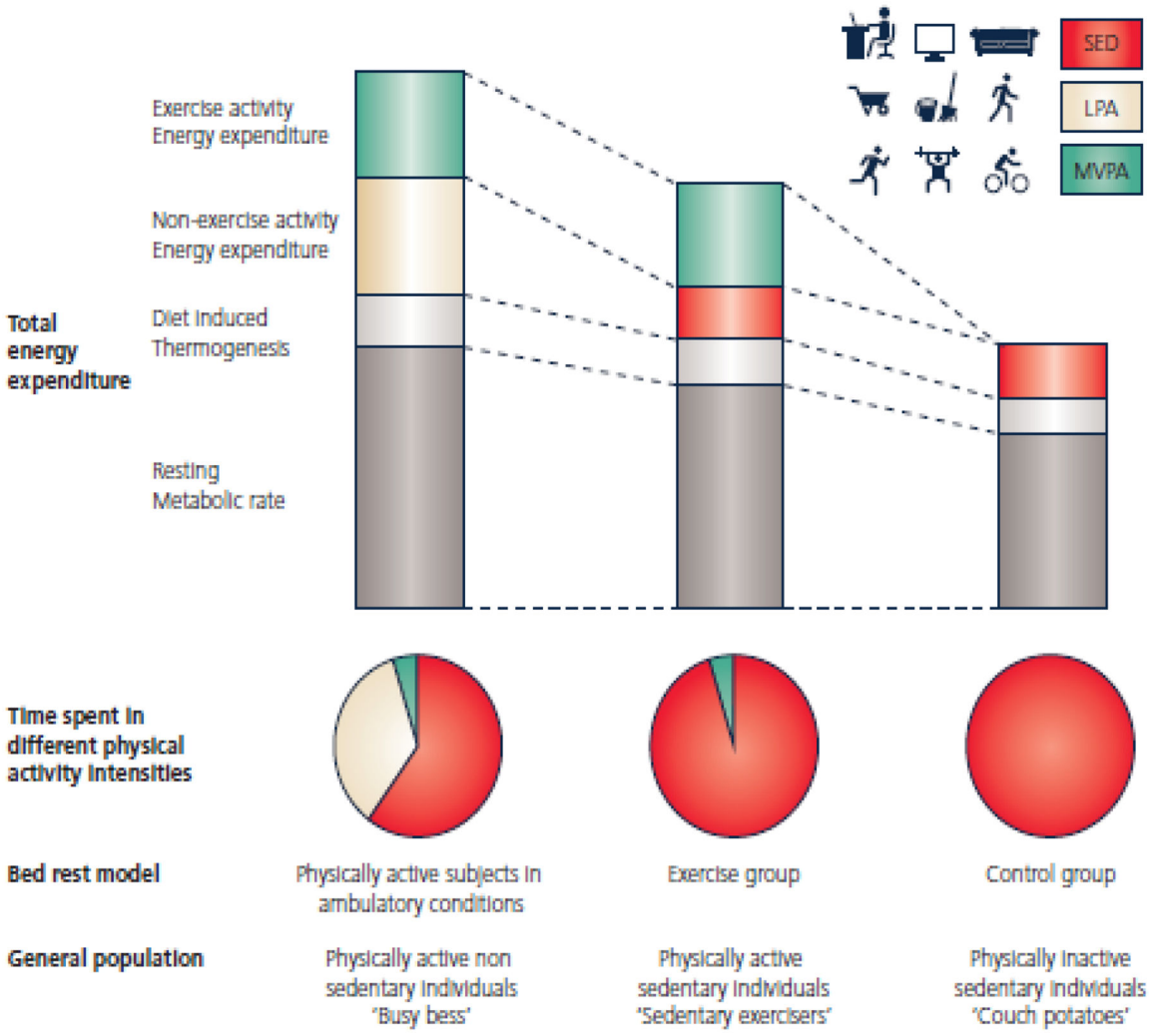

Figure 1: Schematic representation of the components of total energy expenditure during bedrest, conducted with or without exercise training.

Based on total energy expenditure, participants enrolled in bedrest protocols can be compared to the general population. Strict bedrest suppresses both components of physical activity energy expenditure: exercise activity energy expenditure and non-exercise activity energy expenditure. Exercise activity energy expenditure refers to the energy spent in MVPA and/or structured exercise. Non-exercise activity energy expenditure corresponds to any activity of daily life, which are essentially LPA. Participants who are subjected to moderate to vigorous exercise training along with bedrest maintain high exercise activity energy expenditure mainly due to MVPA. However, they are sedentary with very low levels of non-exercise activity energy expenditure and are lacking LPA. These individuals represent an extreme but unique model of “sedentary exercisers”, i.e. physically active yet sedentary people. Strict bedrest leads to a decrease of both MVPA and LPA while increasing SB. These bedrest individuals represent a model of the modern physically inactive sedentary individuals. SED: sedentary activities; LPA: light-intensity physical activity; MVPA: moderate-to-vigorous physical activity. Adapted from Bergouignan et al 2010.

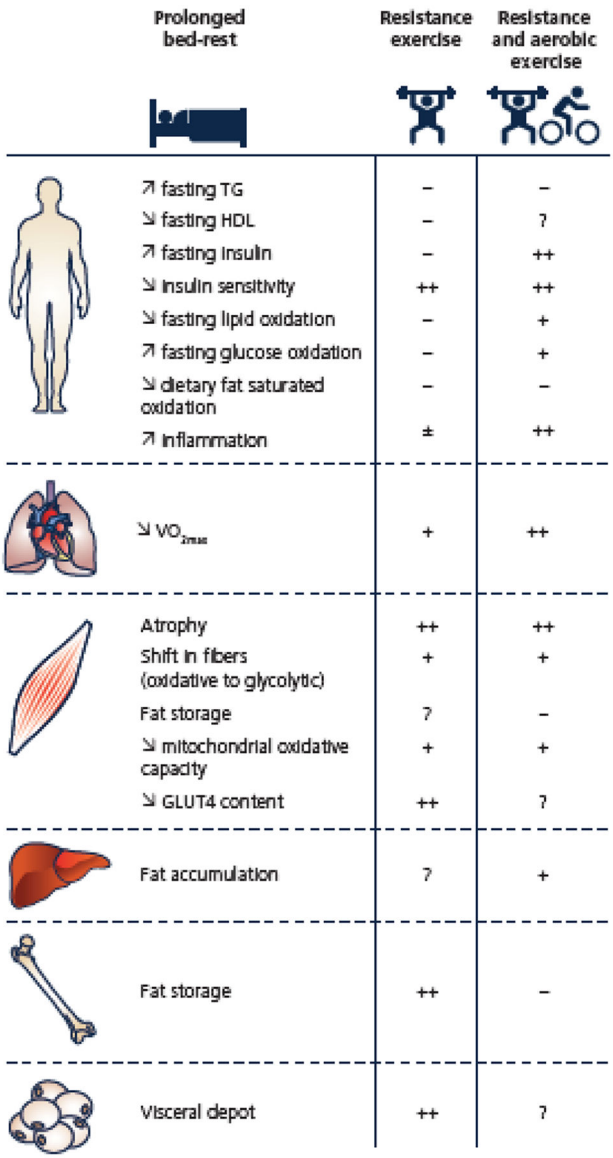

Figure 2: Preventive effect of exercise (resistance exercise or resistance plus aerobic exercise) against the bedrest-induced physiological and metabolic alterations.

− : no effect; + : partially protected; ++ : fully protected; ?: no data available; ± : no consensus.

Table 1:

Summary of the exercise training protocols tested during bedrest studies

Publication	Study name Duration of BR Sample size	Exercise modalities	Estimated duration of MVPA	Estimated energy cost
Resistance exercise				
Bergouignan A. et al. 2006 Fernandez-Gonzalo R. et al. 2020 Irimia J. et al. 2017 Rudwill F. et al. 2013 Trappe S. et al. 2004	LTBR 2001–2002 90 d HDT-BR n=18 ♂	35 min every 3 d during BR on flywheel ergometer. Progressive warm-up + 4×7 max concentric/eccentric squat + 4×14 in calf press. 2 min rest between sets and 5 min between EX.	82 min MVPA/wk 12 min MVPA/d	8 MET.h/wk 1.2 MET.h/d
Brooks N. et al. 2014	28 d HDT-BR n=31 ♂	1 h/d, 6 d/wk. Target intensity: 70–80% of 1RM as estimated by the OMNI rating of perceived EX 10 category scale. 7 to 8 REX targeting major muscle groups during each session. Lower body (squats, single leg squats, diagonal jump, calf raise, single-leg hip extension, leg curl, single-leg hip abduction) and upper body (pull-ups, pull-over, triceps press, chest fly, shoulder press, biceps curl, upright row, lateral arm raise) EX were performed on alternating days.	360 min MVPA/wk 51 min MVPA/d	36 MET.h/wk 5.2 MET.h/d
Ferrando A. et al. 1997	14 d HDT-BR n=6 ♂	Squat on horizontal leg-training device every 2 d. 3×12 squats, training volume progressively increased to reach 5×8 squat at session 3 till the end of BR.	?	?
Guinet P. et al. 2020 Kenny H. et al. 2017 Kenny H. et al. 2020	MNX 21 d HDT-BR n=12 ♂	5 sessions of EX, on leg press machine with a vibration platform (8 mm peak-to-peak, 25 Hz): bilateral squats (10 rep, 75% 1-RM, 8 s/rep), single heel raises (×1.3 body weight, contractions performed as fast as possible until fatigue) and bilateral heel raises (×1.8 body weight, contractions performed as fast as possible until fatigue). A 5% load adjustment was made based on the ability of volunteers to complete the set of EX.	5–15 min MVPA/wk 0.7–2.1 min MVPA/d	0.5–1.5 MET.h/wk 0.01–0.2 MET.h/d
Moriggi M. et al. 2010	BBR1 55 d HDT-BR n=12 ♂	2 bouts/d of EX (6min each) of RVE at preset frequencies ranging from 19 at the beginning to 25Hz. Total of 89 sessions. 1. Squatting EX: Knees were extended from 90° to almost full extension in cycles of 6s for each squat (knee extensors). 2. Heel raises: With knees almost extended, heels were raised to fatigue. Only then, brief rests (< 5s) were allowed with the entire foot on the vibration platform in order to recover, and subjects started to raise their heels again (foot plantar flexors). 3. Toe raises: Similar to 2, but toes were raised instead of heels (foot dorsi-flexors). 4. “Kicks”: With the same loading as in 1–3, knees were extended as quickly and forcefully as possible. The platform was struck with the balls of the feet, and legs rested on the Galileo Space framework in between the kicks. This was done 10 times with 10s of rest inserted.	36 min MVPA/wk 5.1 min MVPA/d	3.6 MET.h/wk 0.5 MET.h/d
Belavy D. et al 2014 Trudel G. et al. 2012	BBR2–2 60 d HDT-BR n=24 ♂	3 d/wk: 1. Bilateral leg press (~75–80% of pre-bed-rest max voluntary contraction); 2. Dingle-leg heel raises (~1.3 times body weight); 3. Double leg heel raises (~1.8 times body weight); 4. back and forefoot raise (performing hip and lumbar spine extension against gravity with ankle dorsiflexion, but with ~1.5 times body weight applied at the shoulders). The RVE group performed the same exercises as the REX group, except that whole body vibration was applied. The corresponding vibration parameters were as follows: 1. frequency 24 Hz, amplitude 3.5–4 mm, and peak acceleration ~8.7 g, where g ~ 9.81 ms^{-2}; 2. frequency 26 Hz, amplitude 3.5–4 mm, and peak acceleration ~10.2 g; 3. frequency 26 Hz, amplitude 3.5–4 mm, and peak	15.8 min MVPA/wk 2.3 min MVPA/d	1.6 MET.h/wk 0.2 MET.h/d

Publication	Study name Duration of BR Sample size	Exercise modalities	Estimated duration of MVPA	Estimated energy cost
		acceleration ~10.2 g; 4. frequency 16 Hz, amplitude 3.5–4 mm, and acceleration ~3.9 g		
Combined resistance and aerobic exercise				
Bergouignan A. et al., 2009 Bergouignan A. et al., 2010 Lee SM. et al., 2014 Mutin-Carnino M. et al., 2013 Rudwill F. et al., 2015 Salanova M. et al., 2008 Trappe T.A. et al., 2007 Trappe S. et al., 2007 Trappe S. et al., 2008 Trudel G. et al., 2009	WISE 60 d HDT-BR n=16 ♀	REX: 35min every 3 d, 4×7 max concentric/eccentric squat + 4×14 in calf press. AEX: 50min every 2 d, 50min in lower body negative pressure vertical treadmill at 40–80% pre-bedrest VO_2max	247 min MVPA/wk 35.3 min MVPA/d	33.1 MET.h/wk 4.7 MET.h/d
Krainski F. et al., 2014	35 d HDT-BR n=27 ♂/♀	REX: 25–30min 2 d/wk. 2×8–12 of lower body exercises (leg press, plantar flexion, knee flexion, hip flexion, and hip abduction) and 1×8–12 of upper body EX (shoulder press, elbow flexion and extension, chest press, pullovers, and abdominal crunches) were performed in the supine position, loads were adjusted weekly to reach muscle fatigue during each set of EX. After 5 wk of BR, 2×20 plantar flexion exercises on each leg 2/d (6–8min) against an elastic band were added for all remaining subjects in EX group. AEX: 6 d/wk. During each week of BR, subjects completed 1 recovery (low intensity, typically <70% max HR), 2 base (moderate intensity, between 70–80% max HR), 1 MSS (vigorous intensity, 80–90% maximal HR), and 2 interval sessions (high intensity, 90–95% max HR or above), each lasting a total of 30 – 46 min and separate warm-up/cool-down phases lasting 5 min each. Intervals consisted of 6 cycles of 3 min at 90–95% of max HR, followed by 3 min at recovery pace.	381 min MVPA/wk 54.4 min MVPA/d	49.5 MET.h/wk 7.1 MET.h/d
Ploutz-Snyder L. et al. 2018	70 d HDT-BR n=26 ♂	REX: 3 d/wk. 3×4 supine lifts (squat, leg press, unilateral leg curl, and heel raise); squats and leg press were each performed using a standard shoulder-width stance, single-leg stance, or wide-leg stance on a rotating basis. Training followed a nonlinear periodized model in which load and repetitions were varied on a daily basis to optimize adaptations. AEX: 6 d/wk. Alternating days of continuous cycle EX for 30 min at 75% of VO_2peak (3 d/w) with interval treadmill sessions of 30s, 2min, or 4min intervals (3 d/wk) at nearly max intensity.	314.5 min MVPA/wk 45 min MVPA/d	40 MET.h/wk 5.7 MET.h/d
Ward K. et al. 2020 (In press)	RSL 60 d HDT-BR n=23 ♂	48 sessions including 4 types of training sessions based on varying CMJ and repetitive hops between 80–90% of BW during 1.5–3min preceded by a warm-up and 3 max CMJ at 80% of BW.	17.5 min MVPA/wk 2.5 min MVPA/d	2.6 MET.h/wk 0.4 MET.h/d

HDT-BR: 6° head-down tilt bedrest; d: days; wk: week; max: maximal; BW: body weight; CMJ: countermovement jump; EX: exercise; REX: resistive exercise; AEX: aerobic exercise

Table 2:

Summary of the acute metabolic health effects of light-intensity physical activity from experimental laboratory-controlled studies

Publication	Sample size and characteristics	Study design Study conditions	Primary results
Studies investigating light-physical activity compared to sitting			
Bailey et al. 2015	N=10 (3♀/7♂) BMI: 26.5 ± 4.3 kg/m^2 Non-insulin resistant	Cross-over (5h/condition) 1) Uninterrupted Sitting 2) Sit + 2min stand every 20min 3) Sit + 2min LIW every 20min	Plasma glucose AUC: LIW < sitting and standing; standing vs. sitting: NS Blood pressure: No between-conditions difference Plasma lipids: No between-conditions difference
Benatti et al. 2017	N=14 ♂ BMI kg/m^2: 24.9 ± 4.3 kg/m^2 Non-insulin resistant	Cross-over (27h/condition) 1) Uninterrupted Sitting 2) Sit + 15min stand every 30min 3) Sit + 30min MIW 4) Sit + 30min MIW and 15min stand every 30-min	Postprandial plasma glucose iAUC: standing < sitting; MIW vs sitting: NS
Dempsey et al. 2016b	N=24 (10♀/14♂) BMI: 33.0 ± 3.4 kg/m^2 Type 2 diabetes	Cross-over (8h/condition) 1) Uninterrupted sitting 2) Sitting + 3min LIW every 30min 3) Sitting + 3min resistance activities every 30min	Blood pressure: LIW < sitting Noradrenaline concentration: LIW < sitting
Duvivier et al. 2017a	N=24 (11♀/13♂) BMI: 29.0 ± 2.0 kg/m^2 Non-insulin resistant	Cross-over (4 days/condition) 1) Sit 13.5h/d, stand 1.4h/d, LIW 0.7 h/d 2) Sit 7.6h/d, stand 4.0h/d, LIW 4.3h/d	OGTT insulin AUC: LIW < sitting Insulin sensitivity (Matsuda index): LIW < sitting Fasted lipids: LIW < sitting Fasted lipoproteins: LIW < sitting Diastolic blood pressure: LIW < sitting
McCarthy et al. 2017	N=34 (18♀/16♂) BMI: 23.8 ± 6.1 kg/m^2 Non-insulin resistant	Cross-over (7.5h/condition) 1) Uninterrupted Sitting 2) Sit + 5min LIW every 30min	Plasma glucose iAUC: LIW < sitting Plasma insulin iAUC: LIW < sitting
Pulsford et al. 2017	N=25 ♂ BMI: 24.9 ± 4.3 kg/m^2 Non-insulin resistant	Cross-over (7h/condition) 1) Uninterrupted sitting 2) Sit + 2min stand every 20min 3) Sit + 2min LIW every 20min	Postprandial plasma glucose AUC: LIW < sitting Postprandial plasma insulin AUC: LIW < sitting Insulin sensitivity (Matsuda index): LIW < standing and sitting
Thosar et al. 2015	N=12 ♂ BMI: 23.7 ± 3.4 kg/m^2 Non-insulin resistant	Cross-over (3h/condition) 1) Uninterrupted sitting 2) Sit + 5min LIW every hour	Flow-mediated dilation: LIW > sitting Shear rate: LIW > sitting
Studies comparing the health effects of light-intensity and moderate-vigorous physical activity to sitting			
Duvivier et al. 2013	N=18 (16♀/2♂) BMI: 22.6 ± 2.6 kg/m^2 Non-insulin resistant	Cross-over (4d/condition) 1) Sit 14h/d 2) Sit 13h/d and 1h EX 3) Sit 8h/d, 4h LPA, 2h stand	OGTT plasma insulin AUC: LPA < sitting and exercise Fasting lipids: LPA < sitting; LPA vs exercise: NS Fasting lipoproteins: LPA < sitting; LPA vs exercise: NS
Duvivier et al. 2017b	N=19 (6♀/13♂) BMI: 30 ± 2.0 kg/m^2 Type 2 diabetes	Cross-over (4d/condition) 1) Sit 14h/d with 4415 steps/d 2) Sit + 1.1h/d EX with 4823 steps/d 3) Sit + stand 2.5h/d and LIW 2.2h/d with 17,502 steps/d	Glycemia (CGMs): LIW < exercise Insulin sensitivity index (HOMA2-IR): LIW < exercise
Duvivier et al. 2018	N= 61 (33♀/28♂) BMI: 27.8 ± 4.3 kg/m^2 Non-insulin resistant and type 2 diabetics	Pooled analysis Cross-over (4d/condition) (1) Sit 14h/d (2) Sit + 1h/d MIW (3) Sit + 5–6h/d LIW and standing	Endothelial function: LIW < MIW Insulin sensitivity index (HOMA2-IR): LIW < MIW Plasma lipids: LIW < MIW

BMI: body mass index (kg/m^2); h: hours; d: day; EX: exercise; body mass index; AUC: area under the curve; iAUC: incremental area under the curve; LIW: light-intensity walking; MIW: moderate-intensity walking; OGTT: oral glucose tolerance test; LPA: light-intensity physical activity; CGMs: continuous glucose monitoring system.