The Effects of Breaking up Prolonged Sitting Time: A Review of Experimental Studies

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ABSTRACT

BENATTI, F. B., and M. RIED-LARSEN. The Effects of Breaking up Prolonged Sitting Time: A Review of Experimental Studies. *Med. Sci. Sports Exerc.*, Vol. 47, No. 10, pp. 2053–2061, 2015. **Introduction**: Prolonged time spent in sedentary behaviors (i.e., activities performed while sitting or reclining) has been consistently shown as an independent risk factor for increased cardiometabolic risk and all-cause mortality, whereas breaking up sedentary time is associated with improved cardiometabolic profile. However, there is still great controversy with the respect to what would be the optimal or minimum type, intensity, and frequency of physical activity necessary to revenue such positive outcomes in different populations. **Objective**: In this review, we aimed to discuss the available evidence from prospective experimental studies regarding the beneficial effects of breaking up prolonged sitting time on cardiometabolic risk factors, and the influence of intensity, frequency, and volume of the physical activity replacing sitting. **Methods**: A structured computer-based search on the electronic databases PUBMED and SCOPUS was independently conducted by two researchers. Only prospective intervention studies (controlled and uncontrolled) evaluating the effects of explicitly replacing sitting time with physical activity (including standing) on metabolic parameters as outcomes were included. **Results**: Seventeen studies were included in the review. **Discussion**: The currently available prospective experimental studies do advocate that breaking up sitting time and replacing it with light-intensity ambulatory physical activity and standing may be a stimulus sufficient enough to induce acute favorable changes in the postprandial metabolic parameters in physically inactive and type 2 diabetic subjects, whereas a higher intensity or volume seems to be more effective in rendering such positive outcomes in young habitually physically active subjects. **Conclusion**: Prospective experimental studies provide considerable evidence of the positive effects of breaking up prolonged time spent sitting on metabolic outcomes. However, it seems that the type, intensity, and frequency of physical activity necessary to effectively counteract the detrimental effects of prolonged sitting may differ according to the subjects' characteristics, especially with respect to the subjects' habitual physical activity level. **Key Words:** PHYSICAL INACTIVITY, PROLONGED SITTING, EXERCISE, SYSTEMATIC REVIEW

Prolonged time spent in sedentary behaviors, defined as activities done while sitting or reclining (i.e., TV watching, computer-related activities, driving a car, etc.) (1) has been consistently considered an important risk factor for abnormal glucose and lipid metabolism, type 2 diabetes (T2D), and all-cause mortality independent of moderate-and-vigorous physical activity (MVPA) (17,19,29). For instance, Koster et al. (17) objectively measured sedentary time in 1906 participants from the US nationally representative National Health and Nutrition Examination Survey (NHANES) 2003–2004 and reported that even after adjusting for time spent in MVPA, participants in the highest quartile of time spent on sedentary behavior had a 3.3 times increased risk for all-cause mortality when compared with the participants in the lowest quartile.

This evidence has challenged the current guidelines for physical activity and highlighted the importance of not only stimulating MVPA but also reducing sedentary time. In line with this, cumulative evidence from observational studies suggests that breaking up the long periods spent in sedentary time is associated with improved cardiometabolic risk factors (11,12,22) and decreased all-cause mortality risk (15), even after accounting for MVPA(5). Notably, this has led to the inclusion of statements on reducing sedentary behavior, more specifically sitting time,

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in the UK and Australian physical activity guidelines (6,8). In the Australian guidelines, it is further recommended that sitting time should be interrupted regularly (6). However, owing to the observational nature of these aforementioned studies, a causal relationship between breaks in sedentary behavior, particularly sitting, and health outcomes cannot be provided.

To establish this potentially causal relationship and elaborate on the most effective way of replacing sitting time, an increasing number of experimental prospective studies have been published. These studies provide exciting data with respect to the positive short-term effects of interrupting prolonged time spent sitting with either light-intensity (i.e., standing and strolling) or moderate-intensity physical activity (i.e., walking and cycling) on the metabolic profile (7,9,10,13,14,16,21,25,26,28). Although the evidence from these studies seems to corroborate most of the observational studies, there is still great controversy with the respect to what would be the optimal or minimum type, intensity, and frequency of physical activity necessary to revenue such positive outcomes.

Thus, the aim of the present review was to summarize and discuss the available evidence from prospective experimental studies regarding the beneficial effects of breaking up prolonged sitting on cardiometabolic risk factors, and the influence of intensity, frequency, and volume of the physical activity replacing sitting time.

METHODS

Search strategy and data sources. A structured computer-based search on the electronic databases PUBMED (free words and MeSH terms) and SCOPUS (free words) on peer-reviewed articles was performed by two researchers (F.B.B. and M.R.L.) on April 20, 2014 (including all available years). The following search was conducted: (trial* OR intervention* OR experiment* OR randomiz*) AND (glucose OR insulin OR triglyceride* OR lipids OR lipid OR cholesterol* OR dyslipid* OR (insulin AND sensitivity) OR (insulin AND resistance) OR (glucose AND *toleran*) OR overweight OR obesity OR adiposity) AND (sitting OR seden*) AND (exercise OR stand* OR walk* OR "physical activity"). The strings were limited to English language. Titles and abstracts were then reviewed and checked for relevance. Relevant full-text articles were then extracted and assessed for inclusion. Finally, reference lists of all included papers were searched by the reviewers for additional relevant studies. All searches were conducted independently by two researchers (F.B. and M.R.L.). Disagreements were resolved by consensus. The search flow is depicted in Figure 1.

Study selection criteria. Studies were prospective intervention studies (controlled and uncontrolled) evaluating the effects of explicitly replacing sitting time with physical activity (including standing) on metabolic parameters as outcomes. Studies were excluded if they (1) did not replace sitting with physical activity, (2) included a multicomponent intervention strategy (e.g., included dietary intervention and physical activity), and (3) did not evaluate the effect of replacing sedentary behavior with a cardiometabolic risk factor outcome.

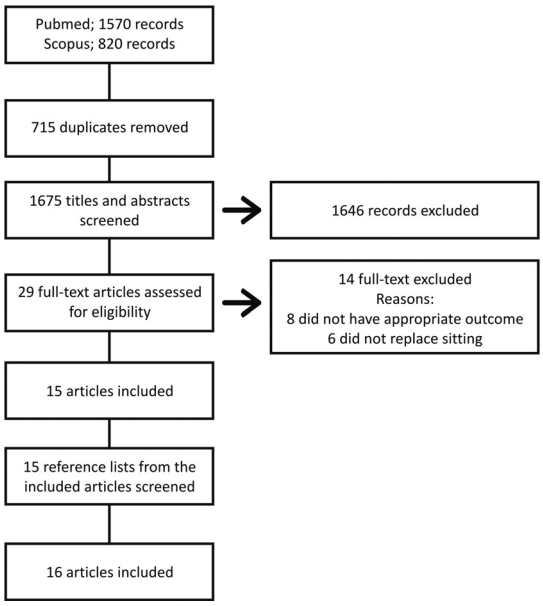

FIGURE 1—Flow chart of search results.

Search results. The search strategy yielded a total of 1675 studies after exclusion of duplicates. Based on titles and abstracts, 1645 studies were excluded. Thus, 29 full-text articles were further assessed for eligibility, from which 16 studies were included in the review. After further revision of all reference lists, one additional study was eligible, yielding 16 studies to be included in the review (Fig. 1).

BENEFICIAL EFFECTS OF BREAKING UP PROLONGED SITTING TIME—EVIDENCE FROM PROSPECTIVE EXPERIMENTAL STUDIES

In the past few years, a number of prospective experimental studies primarily aimed at evaluating the short-term and, to a lesser extent, long-term effects of interrupting prolonged sitting with different types of physical activity on parameters of the metabolic profile have been published. These studies are discussed in succeeding subsections and summarized in Tables 1 and 2.

Short-term studies. Dunstan et al. (9) were the first to demonstrate in a laboratory setting that when compared to 7 h of uninterrupted sitting, breaking up prolonged sitting time with 2-min bouts of light-intensity walking (i.e., $\sim$3.2 km·h^{-1}) every 20 min for 5 h during the postprandial phase reduced both the glycemic and the insulinemic responses to a liquid meal test in 19 physically inactive (i.e., insufficient amount of habitual MVPA) (1) nondiabetic overweight and obese middle-age subjects. Interestingly, when the participants walked at a moderate intensity (i.e., $\sim$6.0 km·h^{-1}),

TABLE 1. Acute effects of breaking prolonged sedentary time.

	Sample (n)	Design	Arms	Outcomes	Results
Altenburg et al. (2)	5 men/6 women	Randomized crossover trial	Prolonged sitting (420 min) (SIT)	Postprandial response during trial: C-peptide, glucose, TG, HDL-chol, LDLchol, T-chol	SIT-CYCLE vs SIT
	Age: 18–24 yr Mean BMI (range): 23.2 (20.1–26.1) kg·m^{-2}	7-d washout period	Prolonged sitting (372 min) + hourly interruptions (8 min of ergometer cycling at 40%–60% of HRR) (SIT-CYCLE)		C-peptide ↓
Bailey and Locke (3)	7 men/ 3 women	Randomized crossover trial	Uninterrupted sitting (300 min) (SIT)	Postprandial response—during trial: TG, HDL-chol, LDL-chol, T-chol, Syst BP, Diast BP	WALK vs SIT
	Mean age (SD): 24 (3) yr	6-d washout period	Sitting (272 min) + 2-min standing every 30 min (STAND)		Glucose AUC ↓
	Mean BMI (SD): 26.5 (4.3) kg·m^{-2}		Sitting (272 min) + 2-min light walking every 30 min (WALK)		WALK vs STAND Glucose AUC ↓ STAND vs SIT No diff.
Buckley et al. (6)	2 men/8 women	Open nonrandomized crossover trial	Uninterrupted sitting (240 min) (SIT)	Postprandial glucose response during the trial: glucose	STAND vs SIT Glucose AUC ↓
	Age (range): men, 22–61; women, 22–59 yr Body weight (range): men, 80–110; women, 45–82 kg	No washout	Standing (240 min) (STAND)	Energy expenditure during the trial	Energy expenditure ↑
Dunstan et al. (8)	11 men/8 women	Randomized crossover trial	Uninterrupted sitting (420 min) (SIT)	Postprandial response—during trial: glucose and insulin	LPA vs SIT
	Mean (SD) age: 53.8 (4.9) yr	6-d washout period	Sitting (402 min) + 2-min low-intensity physical activity (LPA) every 20 min for 5 h (3.2 km·h^{-1})		Glucose AUC ↓ Insulin AUC ↓
	Mean BMI (SD): 31.2 (4.1) kg·m^{-2}		Sitting (402 min) + 2-min MVPA every 20 min for 5 h (5.8–6.4 km·h^{-1})		MVPA vs SIT AUC glucose ↓ AUC insulin ↓ MVPA vs LPA No diff.
Duvivier et al. (9)	11 men/8 women	Randomized crossover trial	4 d of (ex. 8 h of sleep per day);	Postprandial response on the next day: glucose, insulin, TG, HDL-chol, non-HDL-chol, LDL, Apo-A and Apo B	MIPA vs SIT
	Mean (SD) age: 21 (2) yr	10-d wash out period	Sitting (14 h·d^{-1}) + walking (1 h·d^{-1}) + standing (1 h·d^{-1}) (SIT)		Insulin AUC ↓
	Mean (SD) BMI: 22.6 (3.6) kg·m^{-2}		Sitting (13 h·d^{-1}) + walking (1 h·d^{-1}) + standing (1 h·d^{-1}) + MVPA (ergometer—1 h·d^{-1}) (EX)		Fasting Non-HDL chol ↓ MIPA vs EX Insulin AUC ↓ Fasting TG ↓ Fasting non-HDL chol ↓ EX vs SIT
			Sitting (8 h·d^{-1}) + walking (5 h·d^{-1}) + standing (3 h·d^{-1}) (MIPA)		No diff.

(continued on next page)

TABLE 1. *(Continued)*

	Sample (n)	Design	Arms	Outcomes	Results
Howard et al. (13)	11 men/8 women Mean (SD) age: 53.8 (4.9) yr Mean (SD) BMI: 31.2 (4.1) kg·m^{-2} NB: Same sample as Dunstan et al. (8)	Randomized crossover trial 6-d washout period	Uninterrupted sitting (420 min) (SIT) Sitting (402 min) + 2-min LPA every 20 min for 5 h (3.2 km·h^{-1}) Sitting (402 min) + 2-min MVPA every 20 min for 5 h (5.8–6.4 km·h^{-1})	Blood coagulation, blood volume parameters before and after each trial	SIT Plasma volume ↓ Fibrinogen level, hematocrit , hemoglobin, red and white blood cell count ↑ LPA Fibrinogen level → Plasma volume → Hematocrit , hemoglobin, red and white blood cell count → MVPA Fibrinogen level and white blood cell count ↑ Plasma volume, hematocrit, hemoglobin, and red blood cell count →
Kim et al. (16)	9 men Mean (SD) age: 24.0 (4.0) yr Nonobese young adults	Randomized crossover trial > 7-d washout period	Sitting (420 min) Sitting (360 min) + 60 min of MVPA (65% VO_{2peak}) at the end of sitting Sitting (260) min + 9 breaks (self-selected pace ~ 25% $\dot{V}o_{2max}$ but energy matched to the MVPA condition) (LPA)	Postprandial response the next day: TG, glucose	MVPA vs SIT TG AUC ↓ LPA vs SIT TG AUC ↓ MVPA vs LPA TG AUC ↓
Latouche et al. (20)	7 men/1 woman Mean(SD) age: 55.6 (6) yr Mean (SD) BMI: 30.9 (2.9) kg·m^{-2} NB: Subsample from Dunstan 2012	Randomized crossover trial 6-d washout period	Uninterrupted sitting (420 min) (SIT) Sitting (402 min) + 2-min LPA every 20 min for 5 h (3.2 km·h^{-1}) Sitting (402 min) + 2-min MVPA every 20 min for 5 h (5.8–6.4 km·h^{-1})	Gene expression by RNA quantification	LPA and MVPA vs SIT 75 genes differentially expressed, whose biological function are related to: Cellular development ↑ growth and proliferation ↑ Carbohydrate metabolism ↑ Small-molecule biochemistry ↑
Newsom et al. (23)	3 men/8 women Mean age (SD): 28.0 (2.0) yr Mean (SD) BMI: 37.0 (1.0) kg·m^{-2}	Randomized crossover trial ≥7-d washout period	Sitting (480 min) (SIT) Sitting (390 min) + single bout of exercise (~70 min, 50% $\dot{V}O_{2max}$) (EX50) Sitting (375 min) + single bout of exercise (~55 min, 65% $\dot{V}O_{2max}$) (EX65)	Postprandial response immediately after trial: Glucose, insulin Hyperinsulinemic euglycemic clamp and muscle biopsies 19 h after trial	EX50 vs SIT; Insulin sensitivity (Clamp) ↑ EX65 vs SIT; Insulin sensitivity (Clamp) ↑ Muscle glycogen ↓ EX50 vs EX65; Mean FFA uptake (Clamp) ↓
Peddie et al. (26)	42 men/28 women Mean (SD) age: 25.9 (5.3) yr Mean BMI (SD): 23.6 (4.0) kg·m^{-2}	Randomized crossover trial 6- to 13-d washout period	Uninterrupted sitting (810 min) (SIT) Sitting (780 min) + 1 bout of 30-min MVPA (60.5% VO_{2peak}) (CON) Sitting (272 min) + 18 breaks (1 min 40 s total 30 min) (45.6% of VO_{2peak}) (BREAK)	Postprandial response during trial: glucose, insulin, TG, T-chol, HDL-chol, LDL-chol	BREAK vs SIT Glucose iAUC ↓ Insulin iAUC ↓ BREAK vs CON Glucose iAUC ↓ Insulin iAUC ↓ TG iAUC ↑ CON vs SIT No diff

Saunders et al. (28)	11 males/8 females Mean (SD) age: males, 12.9 (0.8) yr; females, 11.3 (0.7) yr Mean (SD) BMI: males 18.7 (4.5) $kg \cdot m^{-2}$; females, 17.4 (2.9) $kg \cdot m^{-2}$	Randomized crossover trial > 7-d washout period	Uninterrupted sitting (480 min) (SIT) Sitting (444 min) + 2-min LPA breaks every 20 min (30% of $\dot{V}O_{2peak}$) Sitting (404 min) + 2-min LPA breaks every 20 min (30% of $\dot{V}O_{2peak}$) + 2 × 20 min MVPA (60% of $\dot{V}O_{2peak}$)	Postprandial response during trial: Insulin, glucose, HDL-chol, LDL-chol, TG	LPA + MVPA vs SIT No diff. LPA vs SIT No diff. LPA + MVPA vs LPA No diff.
Sisson et al. (29)	9 males/9 females Mean (SD) age: 14.8 (2.3) yr Mean (SD) BMI: 22.7 (4.5) $kg \cdot m^{-2}$	Randomized cross-over trial Does not report washout	Uninterrupted sitting (180 min) (SIT) Sitting (45 min) + 3 bouts of 45-min walking every hour (2.4 $km \cdot h^{-1}$, approximately 2 METs) (LPA)	Postprandial response during trial: glucose, insulin, HDL-chol, LDL-chol, and LDL/HDL ratio Endothelial function before and after trial	LPA vs SIT No diff
Thorp et al. (32)	17 men/6 women Mean (SD) age: 42.2 (7.9) yr Mean (SD) BMI: 29.6 (4.0) $kg \cdot m^{-2}$	Randomized crossover trial 7-d washout period	8-h periods on five consecutive days: Uninterrupted sitting (480 min) (SIT) Interchanging standing and sitting every 30 min for 480 min (STAND)	Postprandial response during the first and last day of trial: glucose, insulin and TG	STAND vs SIT Glucose iAUC ↓ Mean glucose iAUC ↓ No within-trial differences (between first and last day) *
Van Dijk et al. (34)	20 men Mean age (SD): 64.0 (1.0) yr Mean (SD) BMI: 29.5 (0.9) $kg \cdot m^{-2}$ T2D subjects	Randomized crossover trial > 7-d washout period	Sitting (720 min) (SIT) Sitting (635 min) + 3 post meal breaks of 15-min strolling (3 METs) (LPA) Sitting (635 min) + 1 postbreakfast break of 45-min cycling (6 METs) (MVPA)	Postprandial response during trial: glucose and insulin; 24-h glycemic control	MVPA vs SIT Hyperglycemic time ↓ Mean 24-h glucose ↓ Glucose iAUC ↓ Insulin iAUC ↓ LPA vs SIT Glucose iAUC ↓ Insulin iAUC ↓ MVPA vs LPA Mean 24-h glucose ↓ Glucose iAUC ↓ Insulin iAUC ↓

Apo, apolipoprotein; AUC, area under the curve; BMI, body mass index; Diast BP, diastolic blood pressure; HDL-col, high-density lipoprotein cholesterol; iAUC, incremental area under the curve; LDL-chol, low-density lipoprotein cholesterol; Syst BP, systolic blood pressure; T-chol, total cholesterol; TG, triglycerides.

TABLE 2. Chronic effects of breaking prolonged sedentary time.

	Sample (*n*)	Design	Arms	Outcomes	Results
Alkahjah et al. (1)	3 males/29 females Mean (SD) age: intervention group, 33.5 (8.7) yr; comparison group, 39.9 (7.2) yr Mean (SD) BMI: Intervention group, 22.6 (2.6) $kg \cdot m^{-2}$; Comparison group, 21.5 (2.6) $kg \cdot m^{-2}$ Healthy office workers	3-month two-arm quasi experimental trial	Intervention group (N = 18): Used sit-stand work stations Comparison group (N = 14); maintain normal work routine	Fasting levels of; HDL-chol, T-chol, TG, glucose	Intervention vs comparison HDL ↑
John et al. (14)	5 males/7 females Mean (SD) age: males, 47.2 (11.8) yr; females, 45.6 (7.8) yr Mean (SD) BMI: males, 33.7 (5.8) $kg \cdot m^{-2}$; females; 34.0 (4.9) $kg \cdot m^{-2}$	Prospective uncontrolled trial (9-month follow-up)	Treadmill desk workstations were installed	BP, resting HR, and fasting blood samples: LDL-chol, HDL-chol, TG, T-chol, VLDL-chol, insulin, glucose, and HB1ac Anthropometrics	LDL Chol ↓ Hb1ac ↓ Waist and hip circumferences ↓

BP, blood pressure; HR, heart rate; VLDL-chol, very low-density lipoprotein cholesterol.

the positive outcomes were similar. Subsequently, in a subsample of patients, Howard et al. (13) reported that breaking up sitting time with either low- or moderate-intensity physical activity attenuated the increase in hematocrit, hemoglobin, and red blood cell count and the decrease in plasma volume observed during uninterrupted sitting, whereas the offsetting of increased fibrinogen levels only reached statistical significance for the low-intensity physical activity breaks. These results suggest that breaking up prolonged sitting may be of importance not only to improving glucose metabolism but also to counteracting the increased risk of thrombosis associated with excessive sitting. Furthermore, if exercise frequency is the same, its intensity does not seem to play a relevant role on postprandial glucose clearance and blood viscosity parameters in overweight and obese physically inactive persons.

Peddie et al. (21) also evaluated physically inactive young healthy normal-weight subjects and showed that bouts of 1 min and 40 s of light-to-moderate exercise (45%–60% $\dot{V}O_{2max}$) every 15 min during 9 h of sitting time lowered the postprandial insulin and glucose responses when compared with 9 h of uninterrupted sitting, suggesting that breaking up prolonged sitting may in fact affect glucose clearance in physically inactive subjects independent of BMI. Remarkably, the same improvement in insulin and glucose responses to meal tolerance tests was not observed when the exercise (matched for intensity and total duration) was performed in a 1-bout fashion before the sitting hours.

Similarly, Duvivier et al. (10) observed the lipid profile and the glucose and insulin responses to an oral glucose tolerance test in young physically inactive participants who underwent three different conditions: prolonged sitting condition (14 $h \cdot d^{-1}$ of sitting + 1 $h \cdot d^{-1}$ of walking + 1 $h \cdot d^{-1}$ of standing); increased light physical activity with a concomitant significant reduction in sitting time (5 $h \cdot d^{-1}$ of walking + 3 $h \cdot d^{-1}$ of standing + 8 $h \cdot d^{-1}$ of sitting); and 1-h MVPA and subsequent prolonged sitting (13 $h \cdot d^{-1}$ + 1 $h \cdot d^{-1}$ of walking + 1 $h \cdot d^{-1}$ of standing). Participants underwent each condition for 4 d and were evaluated on the fifth day. The authors demonstrated that the increased light physical activity protocol was effective in improving the lipid profile and insulin sensitivity when compared with the prolonged sitting condition. Importantly, in the MVPA condition, despite the comparable energy expenditure to the light-activity protocol, no improvements were observed. However, as the monitor used for matching energy expenditure (ActivePal) has not been validated for measuring energy expenditure *per se*, this could have introduced a bias.

Notably, Newsom et al. (20) reported that either moderate-intensity (i.e., 50% $\dot{V}O_{2max}$) or vigorous-intensity (i.e., 65% $\dot{V}O_{2max}$) exercise bouts set to expend approximately 350 kcal performed after 7 h of prolonged sitting did not induce any changes in glucose and insulin responses to a meal immediately after the exercise but similarly increased insulin sensitivity (as assessed by a hyperinsulinemic euglycemic clamp) on the next day when compared to 8 h of uninterrupted sitting in obese physically inactive adult subjects.

Accordingly, Kim et al. (16) showed that breaking up 9 h of prolonged sitting with either 1-h moderate-intensity exercise (i.e., 65% $\dot{V}O_{2max}$) or energy-matched hourly light-intensity walking (25% $\dot{V}O_{2max}$) induced lower triglyceridemic and glycemic responses to a high-fat meal on the next day in nonobese healthy recreationally active young subjects. However, in contrast to the results of Newsom et al. (20), the glycemic response was lower after the moderate-intensity exercise when compared with the light-intensity exercise.

Altenburg et al. (3) evaluated young healthy male and female adults who underwent 8 h of prolonged sitting and, on a different occasion, 8 h of sitting with hourly breaks of 8-min moderate-intensity cycling (50%–60% of the heart rate reserve). In contrast to Dunstan et al. (9), they did not observe any differences in the postprandial glucose and insulin responses between trials, despite lower C-reactive protein levels during the breaking-up sitting condition.

Similarly, Saunders et al. (22) showed that breaking up sitting (8 h) with 2-min low-intensity walks every 20 min, did not impact postprandial responses of lipids, glucose, and insulin when compared with the prolonged sitting trial in healthy young boys and girls (10–14 yr). When participants repeated the same protocol but also performed two bouts of 20-min moderate-intensity exercise, the same results were observed. Moreover, in a similar cohort (i.e., healthy adolescents), Sisson et al. (23) reported no differences in postprandial responses of glucose, insulin, lipids, and endothelial function between 3 h of uninterrupted sitting and breaking up prolonged sitting with three 45-min light-intensity (i.e., 2 METs) walks. It is worth noting that the subjects in these studies had normal weight, and because the habitual physical activity levels of the participants were not provided, they may have been physically active (i.e., sufficient amount of habitual MVPA) (1).

Altogether, these data suggest that in contrast to physically inactive subjects, in physically active subjects, (a) breaking up prolonged sitting may in fact have positive although delayed effects on the metabolic profile, and (b) a higher physical activity intensity or duration, independent of frequency, seems to be more effective in counteracting the detrimental effects of prolonged sitting.

When studying T2D subjects, Van Dijk et al. (28) showed that when compared with a prolonged sitting condition, both a 45-min moderate-intensity continuous exercise (~350 kcal expended) and three 15-min bouts of light-intensity activity (~175 kcal expended) throughout the day were effective in improving the postprandial glucose and insulin responses. Moreover, although both strategies led to improvements in the 24-h glycemic control, the improvement was greater and only reached statistical significance in the MVPA trial. These results suggest that although both light-intensity and moderate-intensity exercise are capable of improving postprandial glucose handling, the long-lasting effects of exercise on glucose homeostasis may occur in a dose-response manner, at least in patients with T2D. Moreover, it seems that in T2D subjects, one bout of MVPA would be sufficient to improve glycemic control. It is possible that T2D subjects may respond differently to different exercise stimulus than nondiabetic subjects. In T2D subjects, data suggest that AMP-activated protein kinase (AMPK) activation is more pronounced at higher exercise intensity compared to healthy lean individuals (24). It could thus be speculated that higher intensity during the study by Van Dijk et al. (28), when compared to the study of Peddie et al, (21), could explain the discrepancies. However, more studies are needed to confirm this hypothesis.

Thorp et al. (26) reported that alternating sitting and standing (i.e., sitting for 30 min and standing for 30 min) over an 8-h period during the postprandial phase for five consecutive days modestly but significantly reduced the glycemic but not the insulinemic response to a liquid meal test in overweight and obese physically inactive subjects. It is worth noting that during the standing time, the subjects were allowed to ambulate, which may have influenced the results, as light walking has been reported to positively affect postprandial glucose (9,21).

Accordingly, Bailey and Locke (4) did not observe any positive effects of 2-min bouts of standing every 20 min on postprandial glucose in 10 normal to overweight participants when compared with 5 h of prolonged sitting. Interestingly, when the subjects underwent 2-min bouts of light walking every 20 min, the glucose response was effectively reduced when compared with the prolonged sitting condition. Once again, since the participants' physical activity level was not provided, it is possible that they were at least fairly physically active. If so, these results indicate that breaking up sitting time with standing may not be a stimulus sufficient enough to improve the metabolic profile in these subjects.

When studying adult desk-based office workers, Buckley et al. (7) observed a 43% lower postprandial glucose excursion and higher energy expenditure (0.83 $kcal \cdot min^{-1}$) with subjects working on a sit-stand desk workstation during 4 h when compared to 4 h of seated desk work. Furthermore, a tendency toward decreased glucose levels overnight after the standing when compared with the sitting day was also reported. Although the authors did not clearly report the amount of time spent sitting and standing in the two conditions of the subjects' physical activity level, these results do suggest that standing may be a stimulus sufficient enough to counteract the hazards of prolonged sitting in office workers.

Chronic studies. In a 9-month prospective uncontrolled trial, John et al. (14) investigated the effects of introducing treadmill desk workstations for 12 overweight and obese adult office workers. The authors reported significant increases in standing (~2 to 3 $h \cdot d^{-1}$) and stepping time (~1 to 1.5 h^{-1}) in detriment of sitting, in addition to significant decreases in waist and hip circumferences, LDL and total cholesterol, and glycosylated hemoglobin. Notably, these positive changes were observed despite no changes in dietary intake.

In a quasiexperimental study, Alkhajah et al. (2) investigated the effects of introducing sit-stand workstations in adult nonobese healthy office workers. After 3 months, the authors reported a significantly reduced time sitting by more than 2 $h \cdot d^{-1}$, which was almost exclusively replaced by standing in the intervention group when compared with the control group (i.e., no intervention). Although no differences were observed with respect to anthropometrics and fasting glucose, a significant increase in high-density lipoprotein cholesterol was observed in the intervention group when compared with the control group. It is worth noting that food intake was not controlled in this study, which may have affected the results.

DISCUSSION

The currently available prospective experimental studies do advocate that breaking up sitting time and replacing it with light-intensity ambulatory physical activity and standing may be a stimulus sufficient enough to induce acute favorable changes in the postprandial metabolic parameters, at least in physically inactive and T2D subjects.

The underlying mechanisms within the muscle responsible for these beneficial effects remain elusive. Latouche et al. (18) have shed some light into this matter using the microarray technique in a subsample of patients involved in the study of Dunstan et al. (9). The authors reported that breaking up sitting time with bouts of either light- or moderate-intensity exercise was associated with changes in the muscle expression of genes involved in cellular development, growth and proliferation, and carbohydrate metabolism. Furthermore, Peddie et al. (21) reported a slightly higher mean respiratory exchange ratio in the regular activity–break intervention when compared with prolonged sitting. This suggests an increased carbohydrate oxidation and, potentially, an increased glucose uptake with frequent breaks in the setting of prolonged sitting.

Despite the convincing evidence of the positive effects of replacing prolonged sitting with light-intensity physical activity in physically inactive subjects, a higher intensity or volume seems to be more effective in rendering such positive outcomes in young habitually, physically active subjects (16). Moreover, there is still great controversy regarding the effectiveness of MVPA in counteracting the hazards of prolonged sitting throughout the day.

In this context, most epidemiological evidence indicates that independent of MVPA practice, a prolonged time spent sitting is still associated with a higher CVD and all-cause mortality risk (17,19,29). Accordingly, the results of Peddie et al. (21) and Duvivier et al. (10) suggest that a bout of MVPA may not be able to counteract the detrimental effects of prolonged sitting throughout the day and further support the importance of constant interruptions of this sedentary behavior, even with light-intensity activities, at least in physically inactive subjects. In contrast, prospective studies have shown that an MVPA bout can effectively prevent the detrimental effects of prolonged sitting on glucose and lipid metabolism in T2D and physically active subjects (16,20,28). It is likely that the different experimental designs (i.e., type, volume, and intensity of exercise), information bias in the epidemiological studies (e.g., overreporting of MVPA) and subjects' characteristics across studies may, at least partially, explain the discrepancies. Moreover, the lack of control of physical activity levels and diet intake before the trials in most of the acute studies (3,4,7,10,20–23,28) may also have introduced important bias, which warrants further randomized controlled trials.

Breaking up sitting time fundamentally implies interrupting prolonged periods of time spent sitting it in environments such as the work place (i.e., desk-bound office work) or at home (i.e., during television watching). Therefore, it is of utmost importance that strategies for "breaking up sitting" are both feasible, that is, capable of interrupting prolonged sitting without disturbing or impairing cognitive capacity, and effective in improving cardiometabolic parameters.

In this context, a recent review by Torbeyns et al. (27) reported that active work stations such as standing or treadmill workstations seemed to positively affect important health parameters while not affecting work efficiency, thus being regarded as feasible and effective vehicles to reduce sitting time in the work place. However, of the 31 studies with adults included in the aforementioned review, only three actually measured the effects of replacing sitting/sedentary time *per se* and concomitantly evaluated metabolic outcomes. Moreover, these studies were small and/or nonrandomized, which may have compromised both the internal and external validity of the findings and need thus to be repeated with in well-designed longer-term prospective experimental studies to confirm the feasibility and effectiveness of these strategies.

In conclusion, epidemiological and prospective experimental studies provide considerable evidence of the positive effects of breaking up prolonged time spent sitting on metabolic outcomes. However, it seems that the type, intensity, and frequency of physical activity necessary to effectively counteract the detrimental effects of prolonged sitting may differ according to subjects' characteristics, especially with respect to subjects' habitual physical activity level. Undoubtedly, there is a great need for more well-designed prospective experimental studies to elaborate on the more feasible and effective (efficient and feasible) physical activity protocol (type, volume, frequency, and intensity) to break prolonged time spent sitting across different population subsets.

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