Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Meta-Analysis of the Relationship Between Breaks in Sedentary Behavior and Cardiometabolic Health

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Objective: The concept of "breaks" in sedentary behavior has emerged as a potential modifier of detrimental effects on adiposity caused by sedentary behavior. The existing research investigating the relationship between breaks in sedentary behavior with adiposity and cardiometabolic health in adults was systematically reviewed and quantitatively synthesized by this study.

Methods: Observational and experimental studies that examined the relationships between the frequency of interruptions of sedentary behavior and markers of adiposity and cardiometabolic health in adults were identified by a systematic search of the literature. A meta-analysis was conducted by using the inverse variance method for experimental trials and a Bayesian posterior probability of existence of an association between breaks with adiposity and cardiometabolic markers for observational studies.

Results: It was revealed by the pooled results from nine experimental studies that breaks in sedentary periods of at least light intensity may have a positive effect on glycemia but not on lipidemia for adults. It is unclear whether this effect is independent of total sitting time. However, the 10 identified observational studies showed an association with breaks, which was independent of total sedentary time, but only for obesity metrics.

Conclusions: The theory that interrupting bouts of sedentary behavior with light-intensity activity might help control adiposity and postprandial glycemia was supported by the evidence. Further investigations with better methods of measuring sedentary behavior patterns and improved study designs are necessary to confirm this preliminary evidence.

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Introduction

Humans spend increasing amounts of time sitting at work and during transportation and leisure time (1). National surveys show that on average adults spend 6-10 h sitting each day (2,3). The activities performed while sitting are clustered under the umbrella term of sedentary behavior (SB) (4). In the last decade, evidence has emerged that the large volumes of SB may have detrimental effects on health (5-8). Much of the momentum for this body of research was initiated by the study of Hamilton et al. (9) who proposed an animal model-based physiological and mechanistic framework for SB by introducing the idea that the cardiometabolic risks of prolonged sitting may not be mitigated by frequent muscle contractions throughout the day.

Currently, several countries have issued specific recommendations to reduce the amount of time spent sitting as part of their physical activity guidelines (10). The advice includes recommendations to "break" sedentary time. This recommendation stems from the seminal study by Healy et al. (11). In this small study, the number of accelerometry-identified interruptions of SB was associated with the markers of obesity and cardiometabolic health, suggesting that in addition to total SB time the pattern of SB time accumulation may be important. The concept of breaks in sedentary time (BSB) is shown in Figure 1. Healy and coworkers (12) argued that more breaks in SB mean fewer extended periods of SB and recommended "breaking sedentary time." As a public health message, this is simple to understand and communicate, and as a result it has gained considerable popularity.

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Currently, there is no such evidence synthesis concerning BSB. The purpose of this study was to systematically review, and quantitatively synthesize, the research investigating the relationship between BSB and obesity markers and cardiometabolic health.

Methods

The methodology was guided by MOOSE (13) and CONSORT (14) recommendations. The review was registered with PROSPERO (CRD42014009749).

Data sources

Electronic database searches of Ovid Medline, Science Direct, and Web of Science were conducted in May 2014, and all articles citing the first published BSB article (11) were tracked through Web of Science and Google Scholar. A Boolean search strategy was developed using keywords relating to SB (sedentary, sitting, and inactivity) and to the concept of BSB (breaks, interruptions, and pattern). In addition, the reference list of all articles meeting the inclusion criteria and authors' personal databases were hand searched. The search was limited to the articles published after Healy et al. (11) and before 31/03/14 and to the studies on adult subject (age, ≥21 years).

Study selection

To be included, the studies had to meet the following criteria: (1) reported a measure of breaks in SB (observational studies) or used a design that included interruptions of SB (experimental controlled studies), (2) reported at least one marker of cardiometabolic health as an outcome, (3) written in English, (4) included human subjects, and (5) were primary research articles.

All screening and reviewing was carried out by two independent reviewers, with the opinion of a third reviewer solicited in cases of disagreement. Retrieved articles were screened first by title, then abstracts. The full text of articles was obtained for the remaining studies and once eligibility was confirmed, data were extracted.

Review and data extraction

Proforma based on MOOSE (13) and CONSORT (14) were used to guide the assessment of the studies' methodological quality. No quality score was derived as per MOOSE recommendations but the quality assessment was used to identify the areas of methodological strengths and weaknesses. Data were extracted from the articles using different templates for observational and experimental studies.

Data synthesis

The results were standardized across studies where possible and tabulated to enable comparison between studies and an overview of findings.

For observational studies, the strength of the associations and statistical significance (p-value and confidence interval) were extracted. For significant results ($P < 0.05$), the strength of the association was also expressed as an unstandardized coefficient, reflecting the change in cardiometabolic outcome corresponding to a change of one BSB per day. In some cases, the cardiometabolic outcomes were expressed as z-scores or dichotomous variables. In these cases, the regression coefficients were excluded from summary table.

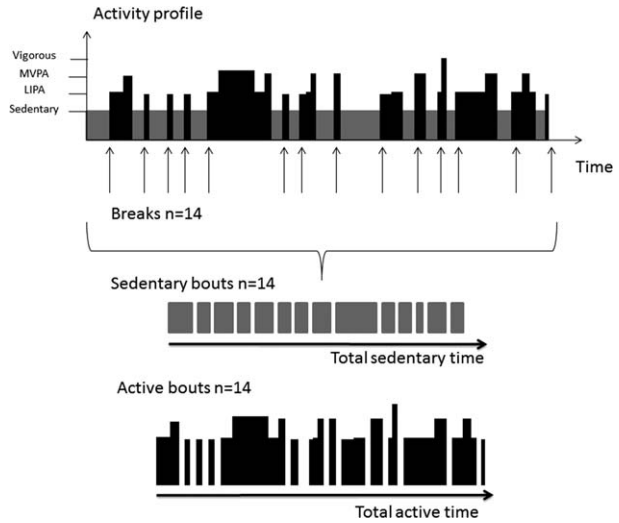

Figure 1 Schematic representation of the concept of breaks in SB.

For observational studies, a Bayesian posterior probability of an association between BSB and cardiometabolic markers was computed to provide a quantitative summary of the state of knowledge. This probability $P(A/Xn)$ is the probability of an association, given the evidence, X, from n studies based on a neutral prior knowledge about the association ($P(A) = 0.5$). It was calculated using Bayes' theorem with the evidence $P(Xn)$ and likelihood $P(Xn/A)$ based on the binomial distributions, assuming no publication bias and that all studies were powered at 80%. The value should be interpreted as a marker of how much uncertainty exists around an association, and the change in knowledge that has occurred as a result of the current evidence. For very heterogeneous results, knowledge will be more uncertain and $P(A/Xn)$ will be close to zero. A probability closer to 1.0 indicates that there is less uncertainty about an association existing. This method was adopted as it was more appropriate for the literature obtained than a standard synthesis of regression (15). For experimental studies, the effect of breaks was meta-analyzed using the inverse variance method modified for crossover trials (16). The analysis is stratified by physical activity intensity of the experimental BSB. As studies expressed change in blood glucose, insulin, lipids, and C-Peptides as either AUC or iAUC over different time scales, the results were normalized to percentage change in the outcome taking into account the time scale.

Results

Article selection results

The search identified 845 articles. Thirteen met all the criteria and were included in the review (Figure 2).

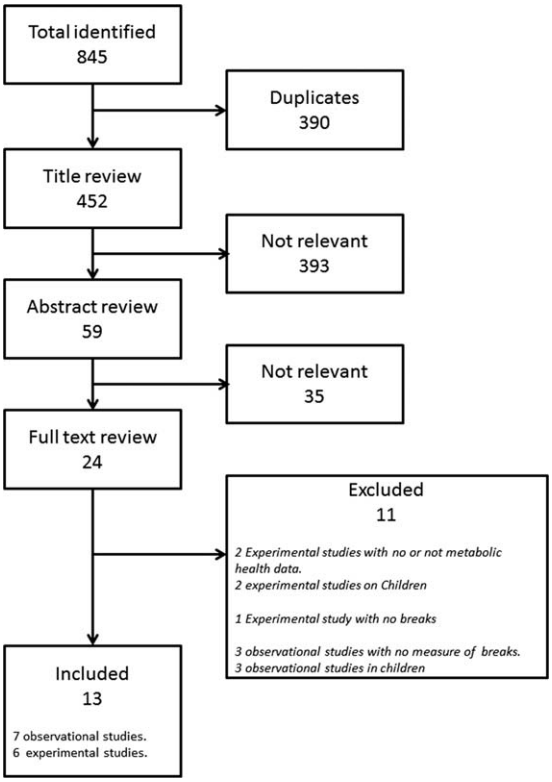

Figure 2 Study selection flow diagram.

Narrative review of study characteristics

Seven articles reported observational studies focusing on the association from an epidemiological perspective, and six articles reported experimental studies focusing on the acute metabolic response to interrupting prolonged sitting. Study characteristics and main findings are summarized in Tables 1 and 2 for observational and experimental studies, respectively. Observational studies were all cross-sectional deriving BSB from accelerometry; either Actigraph (six studies) or Actical (one study). The operational definition of BSB was similar in all studies as a transition from a sedentary state to an active state for a minimum of one accelerometry epoch. The actual epoch duration and associated cut-point for SB varied but were all proportional to 100 counts/min for at least 1 min, that is, when a study used a 15-s epoch, the SB cutoff was set to 25 counts/epoch (Table 2). One study included participants only with recently diagnosed type 2 diabetes (19) and two studies focussed on the participants with known risk of diabetes (21,22). Sampling strategy and sample size varied from relatively small convenience samples (11,20), through to large nationally representative samples (17,18). Six studies investigated the association of BSB with markers of obesity, five with markers of glycemia and lipidemia, and two with inflammatory markers. All the observational studies accounted for difference in total sedentary time in their analysis. Thus, their results could be considered independent of total sedentary time.

Experimental studies were all randomized cross-over trials in adults investigating postprandial response. They fall into two broad categories; comparison of continuous sitting with sitting interrupted by bouts of different intensity activities (standing, light activity, activities of daily living, or moderate- to vigorous-intensity physical activity [MVPA]) (23,27-29), or comparison of the effect of interrupting sitting versus a single bout of activity before or after continuous sitting (24-26). All experimental studies manipulated BSB dimensions (duration, frequency, and intensity) differently. Most manipulated several dimension simultaneously. None fully standardized differences in sitting time and energy expenditure between the uninterrupted sitting condition and the BSB conditions. Also, none of the studies actually manipulated the length of sitting bouts. All studies measured plasma glucose level either through regular blood sampling or through continuous glucose monitoring (25), but a variety of analysis methods were used. Studies also measured plasma insulin levels, serum triglycerides, cholesterol levels, and C-peptides. One study focused on males with type 2 diabetes (25), one on obese subjects (23), and one recruited participants only with impaired glucose tolerance (26).

Quality

Based on the MOOSE criteria, the reporting of the observational studies was generally poor. The main weaknesses were the lack of details of the statistical modeling used, and in particular the treatment of confounding variables, and the lack of attention paid to data loss and sampling biases. Considering the large data loss often encountered while using accelerometry (30), this is a major limitation of most of the studies. Finally, there was also infrequent use of sensitivity analyses among the studies to test the robustness of the results. Healy et al. (17) had the highest quality report, which included a very detailed account of data loss and a sensitivity analysis.

Two studies only (23,28) met all the CONSORT recommendations for reporting trials. All other experimental studies omitted important details. In particular, power calculations and the randomization and blinding procedures were rarely reported. Missing data were not always reported and rarely considered during the statistical analysis. Only the study by Van Dijk et al. (24) explicitly stated how dropouts were handled statistically. Thorp et al. (28) provided the most ecologically valid experiment with a trial over 5 days recreating the work environment.

Results synthesis—observational studies

The key quantitative characteristics of the included studies are summarized in Table 3. For the markers of glucose metabolism, cardiovascular health and inflammation, an association was not detected. The results are relatively homogeneous and the uncertainty is low. The exception to this was from the largest study (17), which found a significant association with C-reactive protein level of 0.0016 mg/dl/break. For the markers of obesity, the results are suggestive of an association with BMI with some certainty. For waist circumference, the results are less homogeneous and the uncertainty is higher. For the markers of obesity, when significant associations were found the actual strength of the relationships were very consistent across studies: -0.05 kg/m^2/break for BMI and -0.17 cm/break for waist circumference.

TABLE 1 Characteristics of observational studies (in chronological order)

Author (Study)	Design	Population	Sample size	Measurement of breaks	Breaks unit	Cardiometabolic outcomes	Analytic strategy	Confounders and covariates included in analysis	Main results
Healy et al. (11) **(AusDiab)**	Cross-sectional	Adults aged 30-87 years	168	Actigraph (1-min epoch); SB defined as <100 counts/min; BSB defined as transition from SB state to active state (≥100 counts/min) for a minimum of 1 min	Breaks per recording time (~7 days)	Waist circumference, BMI, 2-h plasma glucose, insulin level, serum triglycerides, HDL cholesterol, blood pressure	Forced entry linear regression. Breaks as continuous variable.	Age, gender, alcohol intake, employment status, education, household income, smoking status, family history of diabetes, diet quality, MVPA time, SB time, and mean intensity of breaks	Significant beneficial associations of breaks with waist circumference, BMI, 2-h plasma glucose, and triglycerides.
Healy et al. (17) **(NHANES 03-06)**	Cross-sectional	Adults aged >20 years	4,757 (2,118 for fasting glucose), 910 for 2-h plasma glucose)	Actigraph (1-min epoch); SB defined as <100 counts/min; BSB defined as transition from SB state to active state (≥100 counts/min) for a minimum of 1 min	Breaks per recording time (~7 days)	Waist circumference, BMI, 2-h plasma glucose, serum triglycerides, HDL cholesterol, insulin level, HOMA-%B, HOMA-%S, C-reactive protein	Linear regression including sensitivity analysis. Breaks categorized in quartiles. Sample weighted to account for study sampling strategy and selection bias owing to accelerometry dropouts.	Varies between models but included: age, education, smoking, alcohol intake, fat in diet, energy intake, hypertensive, lipidemic, and other CVD medications, family history of CVD and diabetes, diagnosis of diabetes or cancer, poverty-income ratio, marital status, MVPA time, and SB time	Significant beneficial associations of breaks with waist circumference and C-reactive protein.
Bankoski et al. (18) **(NHANES 03–06)**	Cross-sectional	Older adults aged ≥60 years	1,367	Actigraph (1-min epoch); SB defined as <100 counts/min; BSB defined as transition from SB state to active state (≥100 counts/min) for a minimum of 1 min	Breaks per day	Waist circumference, HDL cholesterol, triglycerides, fasting glucose, metabolic syndrome (defined by the Adult Treatment Panel III criteria)	Logistic regression with metabolic syndrome dichotomized. Breaks categorized in quartiles. Sample weighted to account for study sampling strategy and selection bias owing to accelerometry dropouts.	Age, gender, race/ethnicity, education, alcohol consumption, smoking status, BMI, self-reported diabetes and heart disease, MVPA time, and SB time	Significant beneficial association of breaks with waist circumference, HDL cholesterol, triglycerides, and metabolic syndrome.
Cooper et al. (19) **(Early-ACTID)**	Cross-sectional and longitudinal	Adults aged 30-80 years, recently diagnosed with type-2 diabetes	582	Actigraph (1-min epoch); SB defined as <100 counts/min; BSB defined as transition from SB state to active state (≥100 count/min) for a minimum of 1 min	Breaks per day	Waist circumference, HDL cholesterol, insulin level, HOMA-IR	Linear regressions used to investigate cross-sectional association at baseline and at 6 months, and longitudinal association between baseline breaks and metabolic outcomes and breaks at 6 months. Breaks entered as continuous variable.	Age, gender, current smoking status, family history of diabetes, deprivation score, lipid-lowering or diabetes medication, MVPA time, and SB time	Breaks associated with lower waist circumference. Weak association with HDL-cholesterol. Baseline breaks did not predict any metabolic variables at 6-month follow-up. No change was seen in sedentary time or BSB between baseline and 6-month follow-up.

TABLE 1. (continued).

Author (Study)	Design	Population	Sample size	Measurement of breaks	Breaks unit	Cardiometabolic outcomes	Analytic strategy	Confounders and covariates included in analysis	Main results
Oliver et al. (20) **(The Pacific Islands families)**	Cross-sectional	Children aged 6 years and their mother's mean age 34.7 years	126 children and 108 mothers	Actical (1-min epoch); SB defined as <100 counts/min; BSB defined as transition from SB state to active state (≥100 counts/min) for a minimum of 1 min	Breaks per hour	Waist circumference	Forced entry linear regression with factors entered using Wald's criteria. Breaks categorized in quartiles.	Age, gender, wear time, and SB time	No significant association found.
Henson et al. (21,22) **(Pooled data from Walking Away from Type 2 Diabetes Study and Project STAND)**	Cross-sectional	Adults (mean age, 58.4 years) with known risk of diabetes	878	Actigraph GTX3 (15-s epoch); SB defined as <25 counts/15 s; BSB defined as transition from SB state to active state (≥25 counts/15 s) for a minimum of 15 s	Breaks per day	Waist circumference, BMI, impaired fasting glucose, 2-h plasma glucose, HbA1c, triglycerides, HDL cholesterol, total:HDL cholesterol ratio	Forced entry linear regression with breaks entered as continuous variable. Sensitivity analysis to investigate effect of 15-s epoch versus common 1-min epoch.	Age, gender, smoking status, ethnicity, social deprivation, lipid-lowering and beta-blocker medication, family history of type 2 diabetes mellitus, wear time, MVPA time, and SB time	Significant beneficial association of breaks with waist circumference, BMI, and 2-h plasma glucose (not independent of BMI).
Henson et al. (21,22) **(Walking Away from Type 2 Diabetes Study)**	Cross-sectional	Adults (mean age, 63.6 years) at high risk of diabetes	558	Actigraph GTX3 (15-s epoch); SB defined as <25 counts/15 s; BSB defined as transition from SB state to active state (≥25 counts/15 s) for a minimum of 15 s	Breaks per day	C-reactive protein, adiponectin, leptin, interleukin-6	Linear regression. Breaks entered as continuous variable. Sensitivity analysis to ascertain the influence of adiposity, glycemia measurement, and C-reactive protein level.	Age, gender, smoking status, ethnicity, social deprivation, antihypertensive, lipid-lowering, aspirin, or nonsteroidal anti-inflammatory medication, family history of diabetes, wear time, MVPA time, and SB time	No significant association.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HOMA-%B = steady-state beta-cell function; HOMA-IR, homeostasis model assessment insulin resistance; HOMA-%SI insulin sensitivity; LIPA, light-intensity physical activity; MVPA, moderate to vigorous physical activity; NHANES, National Health and Nutrition Examination Survey; SB, sedentary behavior.

TABLE 2 Characteristics of experimental studies (in chronological order)

Author	Design	Details	Population	N	Measurement	Confounders	Main results	Randomization
Dunstan et al. (23)	Randomized crossover trial	3 period × 3 conditions: 1) Uninterrupted sitting for 7 h 2) Sitting interrupted every 20 min by 2 min of light walking (14 breaks) 3) Sitting interrupted every 20 min by 2 min of brisk walking (5.8-6.4 km/h) (14 breaks)	Overweight and obese adults (11 males), aged 45-65 years	19	Serum/plasma glucose and insulin	Standardized meals on set schedule. Energy expenditure (accelerometry) monitored 48 h before trial. Age, gender, and weight.	Compared to sitting (condition 1) the postprandial insulin and glucose response was significantly reduced by light walking breaks (glucose, 24%; insulin, 23%) and brisk walking breaks (glucose, 30%; insulin 23%).	Block randomization by gender, computer-generated, analyst and statistician blinded, Consort Standards
Peddie et al. (24)	Randomized crossover trial	Three conditions in six random orders: 1) Uninterrupted sitting for 9 h 2) 30 min brisk walking then sitting 3) Sitting interrupted by 18 breaks of 1 min 40 s of brisk walking (total of 30 min walking)	Adults, mean age 25.9 years (SD = 5.3) (28 males)	70	Serum/plasma glucose, insulin, and triglycerides	Standardized meals on set schedule. Calorie intake (24-h food diary). Asked to avoid physical activity for 3 days prior to trial. Analyzed as intention to treat.	Compared to condition 1 and condition 2, the postprandial insulin and glucose response was significantly reduced by condition 3 (walking breaks at estimated intensity of 65% VO_{2max}) (glucose, 39%; insulin, 26%); no significant effect of breaks on triglycerides.	Computer-generated randomization
Van Dijk et al. (25)	Randomized crossover trial	Three conditions each lasting 3 days: 1) Uninterrupted sitting for 11 h 2) 3 × 15 min of ADL (∼3 MET) after each meal 3) 1 × 45 min of moderate-intensity cycling (∼6 MET) after breakfast	Adult males with type 2 diabetes aged 64 years (SD = 1)	20	24-h glycemic profile (continuous glucose monitoring), plasma insulin and glucose, and HbA1c	Standardized meals on set schedule. Strenuous activity restriction in the 48 h prior to trial. Analyzed with general estimating equations.	Single bout of exercise, but not ADL, significantly reduced daily prevalence of hyperglycemia and postprandial response. Single bout of exercise and ADL significantly reduced cumulative glucose over three meals (35 and 17%, respectively). Single bout of exercise and ADL reduced plasma insulin concentration (17 and 33%, respectively).	Not reported

TABLE 2. (continued).

Author	Design	Details	Population	N	Measurement	Confounders	Main results	Randomization
Holmstrup et al. (26)	Randomized crossover trial	Three conditions: 1) Uninterrupted sitting for 12 h 2) 1 h of morning continuous moderate to vigorous exercise followed by sitting for 11 h 3) Sitting, interrupted hourly by 5 min of moderate to vigorous exercise (12 breaks)	Adults with impaired glucose tolerance aged 18-35 years	11	Serum/plasma glucose, insulin, and C-peptides	Standardized meals on set schedule. Self-reported diet and physical activity. Structured exercise prevented for 24 h prior to trial.	No significant effect of breaks for glucose response but continuous exercise raised glucose level throughout the day with the difference compared to sitting more pronounced in certain parts of the circadian pattern. Reduced insulin level for both breaks and continuous exercise conditions, with no difference between breaks and continuous exercise. Significant effect of breaks and exercise in lowering C-peptides.	Not reported
Bailey and Locke (27)	Randomized crossover trial	Three conditions: 1) Uninterrupted sitting for 5 h 2) Sitting interrupted every 20 min by 2 min of standing (14 breaks) 3) Sitting interrupted every 20 min by 2 min of light-intensity treadmill walking (3.2 km/h) (14 breaks)	Adults, mean age 24.0 years (SD = 3.0) (seven males)	10	Serum/plasma triglycerides, HDL, total cholesterol, glucose and triglycerides, and blood pressure	Standardized meals on set schedule. Structured exercise, alcohol consumption, and smoking prevented for 24 h prior to trial.	Compared to sitting (condition 1), the postprandial glucose response was significantly reduced by light walking breaks (16.7%); standing breaks had no significant effects. No effect of breaks observed on lipidemia or blood pressure.	Not reported
Thorp et al. (28)	Randomized crossover trial	Two conditions lasting 5 days each 1) Uninterrupted sitting for 8 h 2) Sitting interrupted every 30 min by 30 min of standing + incidental light ambulatory movement (eight breaks)	Obese adults, mean age 48.2 years (SD = 7.9) (17 males)	23	Serum/plasma triglycerides, HDL and LDL cholesterol, glucose, and insulin	Standardized meals on set schedule. Structured exercise, alcohol, and caffeine consumption prevented for 48 h prior to trial. Self-reported food and beverage intake, and objectively monitored physical activity.	Compared to sitting (condition 1), breaks lowered plasma glucose concentration significantly (11.1%); no significant effect on insulin or triglycerides.	Block randomization, computer generated

Abbreviations: ADL, activities of daily living; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent.

TABLE 3 Quantitative summary of observational studies, including Bayesian posterior probability of association, number of studies, total sample size, and unstandardized regression coefficient for studies that found significant associations

Category	Marker	Population	Posterior Bayesian probability of association	Number of studies[a]	*N*	Study	Unit	*B*[b]
Obesity								
	BMI		0.95	2	1,046			
		Adults			168	Healy et al. (11)	kg/m^2	−0.054
		Adults with known diabetes risk			878	Henson et al. (21,22)	kg/m^2	−0.051
	Waist circumference		0.02	6	6,859			
		Adults recently diagnosed with type 2 diabetes (6-month time point only)			528	Cooper et al. (19)	cm	−0.17
		Adults with known diabetes risk			878	Henson et al. (21,22)	cm	−0.17
		Adults NHANES			4,757	Healy et al. (17)	cm	−0.16
Glucose metabolism								
	Fasting plasma glucose		<0.01	4	3,164			
	2-h plasma glucose		0.02	3	1,956			
	HbA1c		0.05	1	878			
	HOMA		<0.01	2	2,646			
	Insulin		<0.01	2	2,646			
Cardiovascular								
	HDL		<0.01	5	6,859			
	Triglycerides		<0.01	4	6,331			
	DBP		<0.01	2	4,925			
	SBP		<0.01	2	4,925			
Metabolic risk								
	Compound		0.82	1	1,367			
Inflammation								
	C-reactive protein		0.23	2	5,544			
		Adults NHANES			4,757	Healy et al. (17)	mg/dl	−0.0016
	Adiponectin, leptin, and interleukin-6	Adults NHANES	0.06	1	558			

[a]The two measurement points in Cooper et al. 2012 were treated as separate studies in this summary if they had different results.
[b]Unstandardized regression coefficient reflecting change in outcome for a change of one break/day, computed only if outcome was expressed as continuous variable and not as a *z*-score.
Abbreviations: DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment, NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure.

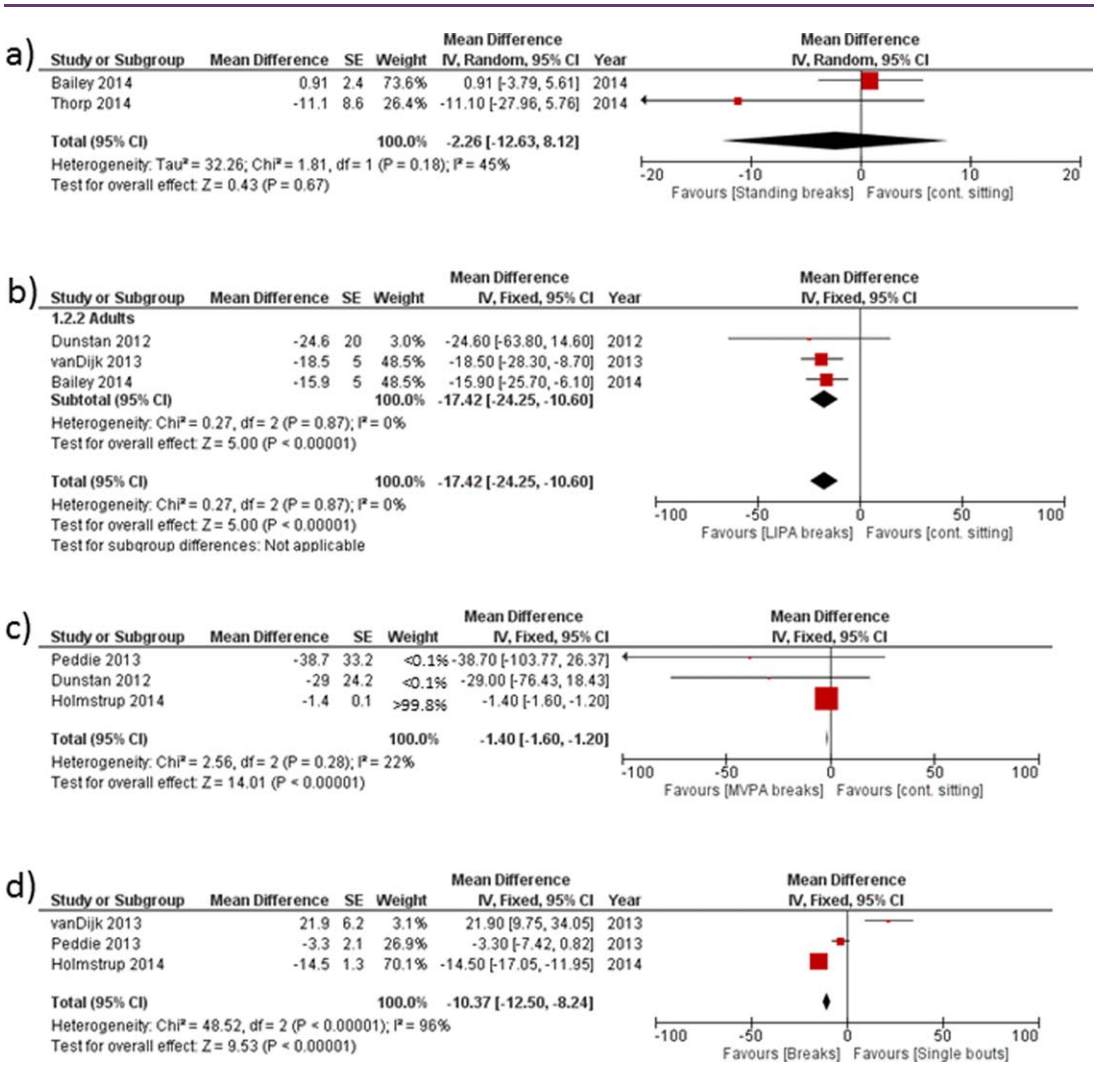

Figure 3 Forest plots of the effect of BSB on blood glucose level (in % change). Continuous sitting is compared to having (**a**) standing breaks, (**b**) LIPA breaks, and (**c**) MVPA breaks. (**d**) Plot shows the meta-analysis of the effect of MVPA breaks compared with continuous sitting plus a single prolonged bout of MVPA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Results synthesis—experimental studies

Glucose. Figures 3a-c show the meta-analysis forest plots of the effect on blood glucose level of different types of BSB compared to uninterrupted sitting. Standing breaks do not appear to produce significant change in blood glucose (−2.26% 95% confidence interval CI [−12.63, 8.12]) compared to uninterrupted sitting (Figure 3a). However, both light-intensity physical activity (LIPA) breaks and MVPA breaks resulted in significant reductions in blood glucose postprandial response (−17.42% [95% CI: −24.25, −10.60] (Figure 3b), and −1.40% [95% CI: −1.60, −1.20] (Figure 3c). In addition, MVPA breaks appear more effective in reducing blood glucose than a single prolonged bout of MVPA (Figure 3d).

Insulin. Based on the four studies (23-26), LIPA and MVPA breaks resulted in significant reductions in insulin levels (−14.92% [95% CI: −20.44, −9.40], and −23.84% [95% CI: −43.46, −4.22], respectively) (Supporting Information Figures S1a,b). Standing breaks were also shown to have significant effect but data from only one study were available (28). MVPA breaks also seemed more effective in reducing blood insulin level than a single prolonged bout of MVPA (Supporting Information Figure S1c).

Lipids. The meta-analysis revealed that BSB do not have a significant effect on triglyceride levels ($P = 0.32$) (Supporting Information Figure S1d). The results for cholesterol could not be pooled but the two studies investigating cholesterol levels all reported null findings (27,29).

C-peptides. The two studies investigating the effect of BSB on C-peptides could not be pooled but both reported significant effects in favor of breaks.

Discussion

Currently, experimental evidence suggests that both LIPA and MVPA BSB have beneficial acute effects on glycemic control, with breaks significantly lowering postprandial glucose and insulin response in adults. There is also tantalizing evidence suggesting that both LIPA and MVPA breaks acutely reduce inflammatory response in adults. However, BSB do not appear to have an acute effect on lipidemia. The meta-analysis showed that interrupting prolonged sitting with short periods of standing does not appear to have sufficient activity intensity to produce acute benefits for any of the cardiometabolic markers. The only study that did find benefits from standing differed from the other studies in that sitting and standing was alternated with equal durations (28).

These results suggest that breaking prolonged sitting with LIPA breaks may be adequate for counteracting the some acute detrimental effects of the SB on cardiometabolic health. In contrast, the evidence from observational studies tends to suggest that there is no detrimental association of prolonged sitting on these same cardiometabolic health markers. Consistent associations were not found between BSB and any of the cardiometabolic markers other than with BMI (Table 3).

One explanation for the discrepancy between experimental and epidemiological study results is that the acute effects of LIPA BSB are short term and do not impact physiology over circadian and longer time scales (25). However, other recent evidence suggests that profound changes in glucose metabolism may occur at the level of gene-expression as a result of breaking prolonged sitting (31), suggesting a carry-over effect. An alternative explanation may therefore be that the true results are obscured owing to methodological and design limitations of the observational studies.

Understanding the effects of BSB is challenging as the number, duration, and intensity of breaks can all be manipulated. Ideally, one of these parameters is tested while controlling the other two. However, this was rarely seen in the studies reviewed (23), leaving a lot of uncertainty as to the cause of observed change in postprandial response. Unfortunately, none of the experimental studies adequately ascertained the dose–response effect of the number of BSB and/or duration of sedentary bouts. Hence, none really focused on the effect of prolonged versus interrupted SBs which was the question raised by the first observational study in the field (11).

The experimental studies instead focused on comparing different intensities of BSB activity levels, or comparing activity in a single bout to several shorter bouts of activity distributed throughout the sitting periods. In this respect, the evidence shows that short frequent bouts of activity seem more effective than a single prolonged bout of activity at reducing blood glucose but not insulin or lipids. This hints to the importance of frequent engagement in LIPA, but does not prove that the benefit is obtained from breaking up SB. The observed effect could also be attributed to the introduction of activity rather than to the breaking of SB. If breaking SB was the key component, then standing breaks would be expected to have similar effect, which was not the case (Figure 3a). Similarly, none of the experimental studies controlled for total energy expenditure or for the total sitting time and therefore it is not clear if the effects reported are owing to a reduction in sitting, the addition of activity, or the action of breaking.

The current lack of clarity is not surprising as this is a new field of investigation. Early studies in other fields of research such as therapeutic exercise similarly initially reported confusing and heterogeneous results. Clearly, further investigation is needed, but a clear picture is likely to emerge only once studies with more carefully planned and precise methodologies are undertaken. It is therefore important to draw some conclusions regarding the limitations of the current evidence and methodologies.

Failure to find an association between BSB and cardiometabolic markers in some studies was not likely to be owing to the issues of statistical power. There was no consistent pattern of larger studies reporting significant results. The measurement of the number of breaks using accelerometry data was a common limitation of all the observational studies. Accelerometers do not precisely record the end of a SB bout, but rather estimate it via a count threshold, which has been shown to have low accuracy (32). This might in part explain the lack of consistent evidence. Future research should consider using measurement instruments such as posture sensors to more accurately detect the end of SB bouts. Longitudinal rather than cross-sectional studies are required to ascertain the effect of long-term exposure. In future, experimental studies looking at acute effects, more effective control of the diverse parameters defining breaks (frequency, duration, and intensity), and accounting for total sedentary time, is needed.

The concept of "breaks" has important limitations that need to be addressed. Breaks do not seem to be a very robust estimate of the pattern of SB and might detract from the fundamental hypothesis set by Healy et al. (11). First, it is very prone to measurement error. Indeed, number of breaks recorded depends on the length of recording period and participant's diurnal pattern. Although this is treated as random error, it is likely that systematic error is involved which is not accounted for in most models. Longer recording periods that are perfectly in phase with the participant's pattern will record more breaks. This is usually the case among more compliant participants who might also tend to be healthier. Analyses usually attempt to correct for this error by including recording time as a covariate in models. Yet, this method is likely to blunt the sensitivity of "breaks" and compound the problem. Using metrics of SB patterns that do not depend so strongly on recording time (33) should therefore be considered.

The second limitation is that "breaks" are as much a metric of frequency of physical activity as of SB (Figure 1). These bouts of activity are most likely to be of light intensity. The association found with obesity markers in the observational studies is therefore also consistent with both the nonexercise activity thermogenesis hypothesis (34) and the reverse causality explanation where heaviness is the reason for fewer activity efforts (35,36).

Finally, although the number of "breaks" is clearly a metric of frequency of sedentary bouts, it is often interpreted as metric of duration of sedentary bouts. The conclusion of Healy et al. (11) and all subsequent studies including experimental studies assumes that more breaks equate to shorter bouts of SB. However, this relies on the relationship between bout duration and frequency being linear, yet studies have shown that the relationship cannot be described by a linear approximation (33,37).

Given these limitations, study designs based on both the metric and the concept of "breaks" may be obscuring the true picture of health

consequences of patterns of activity behaviors. It is unlikely that a simple or linear relationship exists between the pattern of accumulation of SB and the health (37). The results from the acute experimental studies point to a complex physiological response influenced by interactions between several parameters of both activity and SBs. To date, the only proposed mechanism to explain this physiological response is the inactivity physiology theory, which hypothesises that frequent muscular contractions arrest deleterious molecular signals thought to occur during prolonged sitting (9). This theory is likely to be oversimplified as it is the current concept of interrupting sedentary bouts. Yet, "breaks" in SB have appeared as a powerful health message, possibly because of its elegant simplicity.

There are some limitations to this meta-analysis. The literature retrieved did not allow meta-analysis of the association between BSB and health markers through pooled regression coefficient technique, mainly because of the heterogeneity in populations and outcomes reported. Quantitative assessment of publication bias and of statistical heterogeneity was also precluded. Although publication bias may be expected with new topics of research, we noted that studies with both positive and negative (inconclusive) findings have been published. Data from Altenburg et al. (29) could not be included in the meta-analysis of experimental studies as data were unavailable despite contacting the authors repeatedly. However, inclusion of these data would not have changed the overall results.

Conclusion

At present, the evidence for acute or chronic effects of interrupting SB is inconsistent. Available evidence does not support the hypothesis that interrupting long bouts of SB has a beneficial effect on health. However, there is consistent evidence that interruption of sitting with short, frequent bouts of at least LIPA improves postprandial glycemia. Future research should also seek analytically to move beyond the crude concept of breaks and endeavor to understand the pattern of accumulation of SB in more detail.O

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