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Acute Effects of Sedentary Breaks on Vascular Health in Adults at Risk for Type 2 Diabetes: A

Systematic Review

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ABSTRACT

The aim of this systematic review was to evaluate the available evidence regarding the acute effects of interrupting/breaking up prolonged sedentary behavior (SB) on vascular health among individuals at elevated risk for type 2 diabetes (T2D). Searches of MEDLINE, Embase, Web of Science, and Cochrane Library databases were conducted on April 7, 2020. Included studies: 1) examined the effect of breaking up prolonged SB in adults with or at elevated risk for T2D and 2) assessed a vascular health outcome, such as blood pressure (BP), flow-mediated dilation (FMD), pulse-wave velocity, or endothelin-1. A total of 20 articles (17 unique studies) were included. Only 3 studies reported adequate statistical power for the specified vascular outcome. The available evidence suggests that light and moderate intensity activity breaks are effective in acutely lowering BP when compared to prolonged sitting. The small number of studies that included FMD or other vascular outcomes prohibits conclusions regarding the impact of SB breaks on these outcomes. Few studies evaluating the impact of breaking up SB among adults at risk for T2D have included and been adequately powered to examine vascular outcomes, but our preliminary finding, that certain SB breaks improve BP, provides proof-of-concept for this line of inquiry. Future studies should examine both the acute and chronic vascular effects of breaking up SB among individuals most vulnerable to the effects of SB (e.g., older adults, those with T2D), as these individuals are both highly sedentary and at greatest risk of poor health outcomes. (CRD42020183423)

Keywords: sedentary behavior, vascular health, diabetes mellitus, physical activity, blood pressure, obesity

INTRODUCTION

Although the terms are often used interchangeably, sedentary behavior (SB), which is defined as any waking behavior performed in a sitting or lying position and characterized by an energy expenditure ≤ 1.5 metabolic equivalents (METs),¹ is distinct from physical inactivity (i.e., lack of achievement of physical activity guidelines²). SB has significant detrimental long-term health effects, including increased risk of type 2 diabetes (T2D),^{3,4} cardiovascular disease (CVD), and early mortality,^{5,6} even among physically active individuals.⁷ As harmful as SB is in otherwise healthy adults, it presents an even greater concern in individuals with T2D. T2D is a major public health problem, impacting more than 460 million adults worldwide.⁸ Although numerous factors affect the development of T2D, including age, hypertension, lack of physical activity, and genetic factors, elevated body weight alone presents a significant risk factor.⁹ Adults with T2D tend to engage in higher volumes of SB compared to the general population¹⁰ and have frequent cardiovascular comorbidities.¹¹ The combined effects of T2D and SB appear to place individuals with T2D at particularly high risk for poor cardiovascular outcomes.¹²

In addition to the health risks of engaging in a high total volume of SB, research findings suggest that accumulation of SB in prolonged bouts (vs. SB broken up by bouts of physical activity [PA]) is particularly detrimental.¹³⁻¹⁸ In observational studies, prolonged SB has been linked to increased body mass index (BMI), cholesterol, and fasting glucose concentrations.^{13,19,20} Experimental data demonstrate that breaking up prolonged SB (SB breaks) acutely improve postprandial glucose and insulin levels.^{15,21-23} These benefits are more pronounced in individuals with impaired glycemia or T2D,^{24,25} however, the beneficial effects of SB breaks do not appear to be limited to a specific population; similar effects have been observed regardless of age, sex, or BMI.^{15,26,27} Importantly, these associations are observed even

in people who achieve the recommended levels of moderate to vigorous physical activity (MVPA).⁷

Though a growing body of research has documented the beneficial effects of breaking up SB with multiple bouts of PA on glycemic outcomes (e.g., postprandial glucose, insulin), the effects of SB breaks on vascular outcomes (e.g., blood pressure [BP], flow-mediated dilation [FMD], etc.) have received substantially less attention. A systematic review by Saunders *et al.*²¹ synthesized studies examining the acute impact of breaking up SB on glycemic control, triglyceride responses, and vascular function, however only 6 studies included vascular outcomes, and of those, BP was the only vascular outcome in 5 studies. A recent review by Paterson *et al.*²⁸ suggests that the vascular dysfunction of the lower limbs (as measured by FMD) caused by acute exposure to prolonged SB can be prevented by aerobic or resistance activity breaks, however only 6 studies met inclusion criteria. Importantly, existing reviews included primarily healthy young adults while specifically excluding studies of individuals with known metabolic and cardiovascular diseases (e.g., T2D, hypertension). Therefore, it remains unclear if SB breaks influence vascular function in individuals with or at elevated risk for T2D (e.g., impaired fasting glucose, overweight/obesity).

The purpose of the present review is to synthesize the available literature reporting the impact of breaking up prolonged SB on vascular outcomes among adults with or at elevated risk for T2D. Specifically, we address the following research questions: 1) What is the effect of SB breaks on systemic measures (e.g., BP, heart rate), regional measures (e.g., FMD, pulse wave velocity), and blood biomarkers (e.g., epinephrine, endothelin-1) of vascular health? 2) Is there evidence that the type/intensity of break (e.g., standing, light activity, MVPA, resistance

exercise) has differential effects? We hypothesized that SB breaks would have beneficial effects on vascular outcomes among individuals with or at elevated risk for T2D.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the reporting of systematic reviews²⁹ and the review protocol was registered on PROSPERO (CRD42020183423).

Population

Studies of male and female adult participants (age 18 or older) were included. We included studies that focused on participants with T2D or at elevated risk for T2D, which we defined as individuals with impaired glucose tolerance, overweight, or obesity (sample average BMI ≥ 25 kg/m²). Studies that focused specifically on a disease other than metabolic disease (e.g., stroke or spinal cord injury rehabilitation) were excluded due to the potential influence of the disease condition on participant physical function.

Intervention and Comparison Conditions

To be included in the present review, articles must have reported the results of an experimental or quasi-experimental study examining the effects of an intervention targeting breaking up SB on vascular health of human participants. Eligible study designs included randomized controlled trials, interventions without random assignment, and cross-over designs. To be included, the comparator condition had to consist of some form of breaking up or interrupting SB, such as standing or light or moderate intensity PA. No specific limits were placed on the duration of activity or overall intervention period. Studies that examined the effects of detraining or enforced physical inactivity conditions (e.g., bed rest studies) were excluded. We

also excluded studies in which the intervention targeted solely a reduction in total volume of SB and did not report specifically targeting breaking up/interrupting prolonged SB.

Outcomes

Included studies were required to report one or more indicators of central or peripheral vascular health or function, including systemic measures such as BP (systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP]), regional measures such as arterial stiffness (assessed via pulse-wave velocity [PWV]), FMD, or cerebral blood flow, or blood biomarkers (e.g., epinephrine, endothelin-1, nitrates/nitrites, etc.). This broad strategy was used to identify the diversity of vascular measures used in the literature.

Search Strategy

A systematic search was conducted of MEDLINE (via Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions®, 1946 to present), Embase (via Elsevier, Embase.com, 1947 to present), Web of Science Core Collection (via Clarivate Analytics, including Science Citation Index Expanded and Social Sciences Citation Index, 1974 to present), and Cochrane Library (via Wiley, including Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials). Articles reporting the results of intervention studies examining the effects of interrupting or breaking up SB on vascular outcomes among individuals with T2D or at risk for T2D due to impaired fasting glucose, overweight, or obesity were retrieved. The search strategy was developed with the assistance of a research librarian from the University of Colorado Strauss Health Sciences Library. Additional limits (when available) were placed on the searches to restrict the output to articles in English and those that included an adult (age 18 or older) population. No limits were placed on publication date, thus the search included articles published between January 1, 1946

and April 7, 2020. A sample search strategy used for the MEDLINE search is reported in Supplemental Table 1. Similar strategies were used for Embase, Web of Science, and Cochrane Library. Searches of PROSPERO and the Cochrane Database of Systematic Reviews were also conducted to determine if protocols for related systematic reviews had already been published. The reference lists of the selected articles were also reviewed for additional eligible articles.

Study Selection

Review and selection of articles was facilitated by the web-based software platform Covidence (Covidence.org, Melbourne, Australia). The titles and abstracts of all potentially relevant articles were initially screened by one reviewer (MOW or AB). Articles deemed to be potentially relevant were obtained for full-text review and screened by two independent reviewers (MOW and AB). Discrepancies were resolved via discussion to achieve agreement.

Data Extraction

The following data were abstracted from each included article: study purpose, primary and secondary outcomes, characteristics of the study participants (stated target population, sample size, mean age, mean BMI, sex distribution), key components of the intervention (total duration of the condition(s), type of PA, duration and frequency of breaks), and primary findings. We also extracted data on key eligibility and methodological issues in order to evaluate study rigor, including the use of objective measures to assess SB and PA, menopausal status, washout period, documentation and timing of testing in relationship to female hormonal cycle, and abstention from MVPA, alcohol, caffeine, and smoking prior to testing. Data were extracted independently by two authors (MOW and AB), with disagreements resolved by discussion to achieve consensus. Total energy expenditure (kcal/kg) during SB breaks was estimated for each condition based on the PA frequency, intensity, and duration data provided by the authors using

the standard MET calculation procedure in the 2011 Compendium of Physical Activities.³⁰

Determination of Methodological Quality and Strength of the Evidence

Risk of bias was assessed using Cochrane's risk of bias assessment tool.³¹ The strength of the evidence was based on assessment of the key domains (quality, quantity, and consistency) identified by the Agency for Healthcare Research and Quality.³² Risk of bias and strength of the evidence were independently evaluated by two authors (MOW and AB). Disagreements were resolved by discussion among the reviewers to achieve consensus.

RESULTS

A total of 7,239 articles were identified through comprehensive searches of MEDLINE ($n=1,260$), Embase ($n=2,372$), Web of Science ($n=2,171$), and Cochrane Library ($n=1,470$). Five additional articles were identified via searches of the reference lists of the included articles. After removing duplicates, 5,034 unique titles/abstracts were screened (Figure 1). A total of 124 articles were selected based on title/abstract for full-text screening. Of these, 20 articles^{33,34,43-52,35-42} representing 17 unique studies met our inclusion criteria.

Characteristics of Included Studies

Characteristics of the included studies are reported in Table 1. Included studies were conducted primarily in the US ($n=6$),^{34-36,43-45,52} Australia ($n=5$),^{40,41,46,48-50} and the UK ($n=4$),^{33,37-39,51} as well as one study each from Spain⁴⁷ and Brazil.⁴²

Sample Characteristics. Participant demographic characteristics varied greatly across the studies. Although the majority of studies ($n=11$) enrolled both young and middle-age adults, one study included exclusively young adults (18-35 years)³³ and five studies (6 articles)^{41,43,48-51} targeted an older adult population. The mean (*SD*) age of participants ranged from 24.3 (3.0)³³ to 70 (7)⁵⁰ years. Eligible studies ranged in size from 9 to 264 participants and included a total of

627 unique participants. The percent of the sample that was female varied from 17%⁵⁰ to 100%.⁴³ The mean (*SD*) BMI of participants ranged from 25.5 (3.2)^{37,38} to 33.0 (3.4)⁴¹ kg/m². Only one of the included studies specifically enrolled participants with T2D.⁴¹ Additional studies targeted participants at elevated risk of T2D due to impaired fasting glucose (*n*=2),^{44,52} elevated BP (*n*=3),^{34,44,52} excess body fat (*n*=1),⁴² and overweight/obesity (*n*=10).^{34,35,50,52,36,40,41,43,45,46,48,49}

Intervention. All but one of the included studies examined the acute effects (4-10 hours) of breaking up SB in laboratory-based crossover randomized controlled trials. The remaining study was a 19-week community-based cluster randomized controlled trial.⁴⁷ Methods of breaking up SB were variable and included standing, light intensity walking, moderate intensity walking, vigorous intensity walking, high intensity interval training, under-desk pedaling, stationary cycling, and resistance training. Studies included at least one and up to three^{36,52} methods of breaking up SB, most commonly light intensity walking (*n*=10 studies)^{33,37,52,38,39,41-43,46,48,51} and standing (*n*=6).^{33-35,43,45,51,52} SB break frequency varied substantially between studies, ranging from breaks every 20 minutes^{33,36,41-43,46} to every 120 minutes.^{37,38} Similarly, the length of each break was also variable, ranging from approximately 1.3 minutes⁴⁴ to 30 minutes.^{34,35,52} In addition to examining the effects of breaking up prolonged SB, a few studies (*n*=3)^{36,42,49,50} also sought to compare the differential effects of one continuous bout of PA to multiple breaks in SB over the course of the intervention period. In every study, SB breaks were compared to a prolonged sitting condition or lack of intervention in the case of the community-based study.⁴⁷

Outcome measures. BP (SBP and DBP) was the most commonly reported vascular outcome, assessed in 16 of the included studies.^{33,34,46-49,51,52,36,39-45} Notably, few studies (*n*=3) were specifically powered for any of the included vascular outcomes.^{36,38,42} Two studies were

powered to evaluate the effects of the intervention on BP^{36,42} and one study was powered to detect changes in superficial femoral artery FMD.³⁸ Although all studies included at least one vascular outcome, most also included glycemic control (e.g., post prandial glucose) as a primary ($n=10$)^{33,36,39,41-44,46,51,52} or secondary ($n=1$)⁴⁸ outcome. Popliteal and brachial artery FMD, calf circumference, cerebrovascular conductance, cerebrovascular CO₂ reactivity, epinephrine, nitrates/nitrites, endothelin-1, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 were each only included in a single study and are therefore not reported on further.

The frequency of measurement of each outcome varied substantially. The most frequent assessment occurred in studies using ambulatory BP monitoring, where BP was recorded every 15 minutes ($n=2$).^{33,36} Most commonly ($n=10$), BP was measured hourly and immediately prior to a SB break.^{33,34,49,35,39,41,42,44-46,48} Three studies (assessing FMD^{37,43} and calf circumference⁴⁵) included pre and post measurements only.

Effect of Break Type on Vascular Outcomes

The effects of various break types on systemic vascular outcomes (i.e., SBP, DBP, MAP, heart rate), sorted by break intensity and observed response, are reported in Table 2. A total of 6 studies evaluated the impact of breaking up prolonged SB with standing on SBP,^{33,34,43,45,51,52} only one of which found a significant decrease in SBP in response to the intervention.⁵²

Similarly, there was no consistent effect of standing breaks on DBP.^{33,34,43,45,52}

Conversely, light and moderate intensity walking resulted in significant reductions in SBP in $n=5/9$ ^{39,41,46,51,52} and $n=2/3$ ^{36,46,49} of the included studies, respectively. Significant reductions in DBP were observed in $n=4/8$ ^{39,41,42,46} studies that evaluated light intensity walking and $n=2/3$ ^{46,49} of those that examined moderate intensity walking. There were no clear patterns

with respect to the effect of SB break type on MAP or HR, with exception that moderate walking and resistance training significantly increased average HR over the measurement period.^{40,44,49}

The effect of different types of breaks on regional vascular outcomes (e.g., FMD, PWV, cerebral blood flow) are reported in Table 3. The most commonly assessed regional vascular outcome was superficial femoral artery FMD ($n=3$).^{38,40,43} There was no clear evidence of the effects of different types of breaks on superficial femoral artery FMD, with significant improvement observed in only one⁴³ of the two studies^{38,43} that examined the effects of light intensity walking on superficial femoral artery FMD. There was no evidence of an effect of SB breaks on PWV or middle cerebral artery blood flow velocity.

The impact of break type on norepinephrine, the only blood biomarker of vascular function included in two or more studies, is reported in Supplemental Table 2. Although light walking and resistance training resulted in decreased norepinephrine in one study,⁴¹ a second study found no effect of moderate intensity walking breaks on this biomarker.⁴⁹

Rigor of Research

Key methodological considerations related to eligibility criteria and study conditions, and if they were adequately addressed, are reported in Table 4. Some of the common issues identified were that few studies included objective measurement of PA and SB when evaluating whether a potential participant met eligibility criteria for sedentariness and physical inactivity ($n=4$)^{42,48,51,52} and methods of assessment varied substantially (e.g., pedometer, wrist or hip-worn accelerometers). Additionally, menopausal status was not assessed objectively (via follicle stimulating hormone [FSH]) in any of the included studies and was reported in only five of the included studies.^{36,40,42,43,49,50} Regarding the intervention, less than half of the included studies obtained objective SB/MVPA data during each condition ($n=8$)^{34–36,39,41,47,48,51,52} and timing of

testing in relationship to female hormonal cycle was only documented in 5 of the included studies.^{36–39,44,45} Additionally, washout periods between conditions varied substantially (e.g., no reported washout period [i.e., all visits completed in a single 7-day period]^{37,38} visits separated by up to 14 days,^{34,35,41,44} and no reported upper limit on time between visits^{33,36,39,40,45,49,50}) and guidelines regarding abstention from caffeine, alcohol, smoking were inconsistent.

Risk of Bias and Quality of the Evidence

Ratings of risk of bias for the included studies are reported in Supplemental Table 3. Most of the included studies had potential bias related to lack of blinding of participants, personnel, and outcome assessors to experimental condition. Additionally, the presence of bias related to allocation concealment was unclear in most articles. Overall, the strength of the evidence is moderate to suggest a positive effect of light intensity walking and moderate intensity walking on BP, and insufficient for other SB break types and vascular outcomes.

DISCUSSION

Our primary finding is that whereas standing alone was insufficient to acutely influence BP, breaking up prolonged SB with light and moderate intensity PA did result in lower SBP and DBP in adults with overweight/obesity. The data are insufficient to conclude whether other break types, including high intensity aerobic activity or resistance training have similar effects, the long-term effects of SB breaks, or the impact of the specific duration and frequency of the break. We did not find evidence of an effect of SB breaks on PWV and superficial femoral artery FMD, likely in part due to the small number of studies that included these outcomes. Importantly, few of the included studies were adequately powered to evaluate the effects of SB breaks on the reported vascular outcomes, which limits our ability to draw clear conclusions.

Our results are consistent with those reported in a pooled analysis of 4 trials by Dempsey *et al.*, which suggests that light walking breaks effectively lower BP acutely when compared to prolonged sitting.⁵³ The most substantial reductions in BP were observed in individuals with hypertension or prehypertension.⁵³ Limitations in the available data preclude a conclusion about the impact of SB breaks on FMD and PWV in adults at risk for T2D, however the work of Paterson, *et al.*²⁸ suggests that SB breaks may counteract the negative effects of prolonged sitting on lower extremity vascular dysfunction among healthy adults. As norepinephrine was the only blood biomarker of vascular health assessed in two or more studies,^{41,49} the effect of SB breaks on these outcomes is unknown.

Although exercise training is known to have a positive effect on vascular outcomes in individuals with overweight/obesity⁵⁴ and T2D,⁵⁵ the potential unique effects of intermittent breaks in SB vs. one continuous bout of PA on BP, FMD, and other vascular outcomes remain unclear. Only 3 studies (4 articles) directly compared the effects of SB breaks to a single continuous bout of activity (Table 1).^{36,42,49,50} The available data support the conclusion that light and moderate intensity activity breaks have acute, positive effects on BP, similar to those observed with continuous bouts of PA in these studies. This is comparable to what has been observed in studies comparing multiple SB breaks to a single, continuous bout of PA with respect to glycemic outcomes.⁵⁶ A recent systematic review and meta-analysis of 26 studies comparing SB breaks to one bout of PA found that SB breaks moderately attenuated post-prandial glucose, insulin, and triacylglycerol levels, with a small but significant advantage for SB breaks compared to continuous PA when energy expenditure was matched between conditions.⁵⁶ Additional studies are needed to evaluate if the effects of SB breaks are aligned with or different from improvements in vascular outcomes observed with exercise.

An important consideration in the interpretation of these studies is the relative homogeneity of the individuals in which SB breaks have been evaluated. There is a critical gap in understanding the vascular effects of breaking up SB in individuals other than healthy adults. Only one of the included studies specifically enrolled participants with T2D⁴¹ yet individuals with T2D are at highly elevated risk for significant CVD complications. Additionally, few studies enrolled individuals with elevated BP or hypertension. Given that the most robust intervention effects could be expected among individuals who have vascular dysfunction, evaluating methods of breaking up SB in this population is essential.

We identified some limitations with respect to the scientific rigor of the available studies. Importantly, whether some of the included vascular outcomes, such as PWV, are amenable to acute changes in SB is unclear. A wide variety of vascular outcomes have been reported in the literature, and, while we limited our analysis to outcomes assessed in two or more studies, future studies must carefully consider and justify which vascular measures should be included. Additionally, methods to assess key outcomes, including blood pressure and FMD, were quite varied, making comparisons of the magnitude of change across studies difficult. Frequently, studies did not address female hormonal cycle and menopausal status, yet female sex hormones are known to influence cardiovascular outcomes⁵⁷ and responses to PA.⁵⁸ Additionally, few studies included an objective measurement of habitual PA and SB yet being “sedentary” was frequently included in the list of study eligibility criteria. Blinding of study participants and personnel was also a common issue. Though challenging, blinding of personnel and outcome assessors would ultimately increase confidence in the observed differences between interventions. Finally, the small number of studies, diversity of outcome measures, and

variability in the study samples prohibit the examination of dose-response relationships or response in subpopulations of individuals such as older adults or women.

Recommendations and Future Directions: Call to Action

The studies identified in this review were instrumental in laying the foundation regarding the effect of different types of breaks in prolonged SB on vascular outcomes in individuals with overweight/obesity or otherwise at an elevated risk for T2D, but extensive further research needs to be conducted in this area. First, it is critical that well-powered, rigorous studies are conducted to clearly examine the acute effects of breaking up SB on vascular outcomes, especially in populations at risk for vascular disease. Additionally, the relationship between the timing of testing and female hormonal cycle, use of caffeine/alcohol, and smoking must be considered. Researchers should also consider using objective measures such as accelerometry and posture monitors to assess SB and PA pre-intervention to quantify participants' habitual physical behavior. For metabolic studies in humans, including standardized study design components, such as a ≥ 7 -day washout period between a control and intervention period, dietary controls, and matching energy expenditure could help eliminate some of these challenges and facilitate future meta-analyses. It would also be beneficial for the field to standardize the frequency/duration of breaks in SB, but this will require further study to come to consensus. To facilitate this standardization, we have developed a theoretical study design (Figure 2) based on our review and suggestions by Dunstan and colleagues⁵⁹ with key issues that researchers conducting this work should consider.

It is also unclear if the positive effects of SB breaks are sustained or diluted over time. Though acute, highly controlled, laboratory-based studies are important to evaluate the physiological impacts of different types of interventions, translation of these efforts into

community-based interventions is needed to understand the real-world health effects as well as long-term effects of SB breaks on health. Additionally, it is essential to understand if the effects of SB breaks are population-dependent, including if there are sex-related differences in response.⁶⁰ Understanding the effects of SB breaks in older adults with hypertension and T2D is also of importance, as most studies have focused on young, healthy individuals.

Finally, it is important to understand whether the observed effects are due to multiple interruptions in SB or simply the result of an increase in total volume of PA/energy expenditure. Studies should compare light and moderate intensity breaks with matched energy expenditure between intervention groups, as well as investigate if there are differential effects of multiple breaks in SB when compared to a single continuous bout of exercise with the same duration of sedentary and active time. If similar outcomes are observed in light and moderate breaks (i.e., light activity is enough to induce favorable health effects), it could provide an approachable target for increasing PA, particularly among older adults and populations with chronic conditions, where a focus on MVPA may initially seem overwhelming or unattainable.

In summary, although there is some evidence to suggest that breaking up SB with light and moderate intensity walking has beneficial effects on BP for adults with overweight/obesity, the existing data are based on very few studies. The effects of other types of SB breaks (e.g., walking, cycling, resistance training) or impact of light/moderate intensity activity on other vascular outcomes is unclear. Our conclusions are tempered by the caveat that few studies been adequately powered to examine vascular outcomes, individuals with risk factors for T2D other than elevated BMI have rarely been studied, and variability in the type, frequency, and duration of the breaks makes direct comparisons of the effectiveness of different break modalities challenging. Future rigorously designed studies should focus on individuals who are most

vulnerable to the effects of SB, including diverse groups of older adults, office workers, and those with T2D and other risk factors for cardiovascular disease, as these individuals tend to be highly sedentary and at greatest risk of poor health outcomes.

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DECLARATION OF CONFLICTING INTERESTS

The Authors declare that there is no conflict of interest.

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Table 1. Characteristics of included articles ($N=19$ articles representing $N=17$ unique studies).

Study	Country	Sample Characteristics (key descriptors, age [years, $M(SD)$], male/female [n], BMI [kg/m^2 , $M(SD)$])	Design	Intervention Details						Vascular Outcome(s)
				Total Duration	Type of PA	Duration/ Frequency	Number of Bouts	Total Active Time	Estimated Total Energy Expenditure (kcal/kg)	
Bailey et al., 2015 ³³	UK	Healthy adults ($N=10$) Age: 24.3 (3.0) Male/Female: 7/3 BMI: 26.5 (4.3)	Crossover RCT	5 h	Standing	2 min break every 20 min	14	28 min	0.61	SBP DBP
					Light intensity walking (treadmill, 3.2 km/h, 0% grade)	2 min break every 20 min	14	28 min	1.31	
Barone Gibbs et al., 2017, ³⁴ Perdomo et al., 2019 ³⁵	US	Inactive, working-age adults with elevated BP and overweight/obesity ($N=25$) Age: 42 (12) Male/Female: 16/9 BMI: 31.9 (5.0)	Crossover RCT	10 h	Standing (standing desk)	30 min break every 30 min	10	5 h	9.00	SBP ³⁴ DBP MAP HR PWV MCAv ³⁵
Bhammar et al., 2017 ³⁶	US	Healthy, inactive adults with overweight/obesity ($N=10$) Age: 32 (5) Male/Female: 5/5 BMI: 30.3 (4.6)	Crossover RCT	9 h	Submaximal walking (treadmill, 5.3 km/h with grade to elicit mean 56% of VO_2 max)	30 min continuous bout	1	30 min	2.60	SBP* DBP* MAP*
					Moderate intensity walking (treadmill, 4.8 km/h, 0% grade)	2 min break every 20 min	21	42 min	2.72	
					Vigorous intensity walking (treadmill, 4.8 km/h with maximally tolerated grade to elicit mean 68% of VO_2 max)	2 min break every 60 min	8	16 min	1.59	

Study	Country	Sample Characteristics (key descriptors, age [years, $M(SD)$], male/female [n], BMI [kg/m^2 , $M(SD)$])	Design	Intervention Details						Vascular Outcome(s)
				Total Duration	Type of PA	Duration/ Frequency	Number of Bouts	Total Active Time	Estimated Total Energy Expenditure (kcal/kg)	
Carter et al., 2018, ³⁷ 2019 ³⁸	UK	Healthy desk workers employed in office/administrative jobs ($N=15$) Age: 35.8 (10.2) Male/Female: 10/5 BMI: 25.5 (3.2)	Crossover RCT	4 h	Light intensity walking (treadmill, self-selected pace [mean 3.6 (0.9) km/h], 0% grade)	2 min break every 30 min	8	16 min	0.75	MCAv ³⁷ CVC CVR
					Light intensity walking (treadmill, self-selected pace [mean 3.6 (0.9) km/h], 0% grade)	8 min break every 120 min	2	16 min	0.75	SFA FMD* ³⁸ Blood flow Shear rate MAP HR
Champion et al., 2018 ³⁹	UK	Healthy, sedentary adults ($N=24$) Age: male 32 (10.5), female 39.5 (10.3) Male/Female: 12/12 BMI: male 26.6 (4.5), female 24.8 (5.1)	Crossover RCT	6.5 h	Light intensity walking (treadmill desk, self-selected pace [1.2-3.5 km/h], 0% grade)	20 min break every 60 min	6	120 min	4.6	SBP DBP MAP
Climie et al., 2018 ⁴⁰	Australia	Healthy, middle age/older adults with overweight/obesity ($N=19$) Age: 57 (12) Male/Female: 11/8 BMI: 30.6 (3.4)	Crossover RCT	5 h	Resistance exercises (light intensity body weight exercises in standing posture, 3 sets of 20 sec, 3 exercises: half squats, calf raises, gluteal contractions and knee raises)	3 min break every 30 min	10	30 min	1.75	Brachial FMD SFA FMD Blood flow Shear rate Endothelin-1 Nitrates/nitrites VCAM-1 ICAM-1

Study	Country	Sample Characteristics (key descriptors, age [years, $M(SD)$], male/female [n], BMI [kg/m^2 , $M(SD)$])	Design	Intervention Details						
				Total Duration	Type of PA	Duration/ Frequency	Number of Bouts	Total Active Time	Estimated Total Energy Expenditure (kcal/kg)	Vascular Outcome(s)
Dempsey et al., 2016 ⁴¹	Australia	Adults with T2D and overweight/obesity ($N=24$) Age: 62 (6) Male/Female: 14/10 BMI: 33.0 (3.4)	Crossover RCT	8 h	Light intensity walking (treadmill, 3.2 km/h, 0% grade)	3 min break every 30 min	12	36 min	1.68	SBP DBP HR Norepinephrine
					Resistance exercises (light intensity body weight exercises in standing posture, 3 sets of 20 sec, 3 exercises: half squats, calf raises, gluteal contractions and knee raises)	3 min break every 30 min	12	36 min	2.10	
Freire et al., 2019 ⁴²	Brazil	Inactive young adults with excess body fat ($N=25$) Age: 24.4 (3.8) Male/Female: 10/15 BMI: 26.1 (3.4)	Crossover RCT	10 h	High intensity interval training (treadmill, 5 min warm-up at 4 km/h, 10×1 min at 100% of peak treadmill velocity with 1 min passive recovery, and 2 min cool down at 4 km/h, 0% grade)	27 min continuous bout	1	27 min	2.32	SBP* DBP* MAP*
						5 min break every 20 min	6-7	30-35 min	1.75-2.04	
					Light intensity walking (treadmill, self-selected pace [mean 4.5 (0.6) km/h], 0% grade, goal was 10,000 steps)					

Study	Country	Sample Characteristics (key descriptors, age [years, $M(SD)$], male/female [n], BMI [kg/m^2 , $M(SD)$])	Design	Intervention Details						Vascular Outcome(s)
				Total Duration	Type of PA	Duration/ Frequency	Number of Bouts	Total Active Time	Estimated Total Energy Expenditure (kcal/kg)	
Larsen et al., 2014 ⁴⁶	Australia	Inactive middle-age adults with overweight/obesity ($N=19$) Age: 53.8 (1.1) Male/Female: 11/8 BMI: 31.2 (0.9)	Crossover RCT	5 h	Light intensity walking (treadmill, 3.2 km/h, 0% grade)	2 min break every 20 min	14	28 min	1.31	SBP DBP MAP HR
					Moderate intensity walking (treadmill, 5.8-6.4 km/h, 0% grade)	2 min break every 20 min	14	28 min	2.01	
Puig-Ribera et al., 2015 ⁴⁷	Spain	Office workers from targeted university campuses ($N=264$) Age: 42 (10) Male/Female: 93/171 BMI: intervention 25.5 (4.1), control 25.9 (4.7)	Cluster RCT	19 weeks	‘Walk at Work’ intervention - Ramping phase (weeks 1-8): employees challenged to progressively increase movement by 1,000 to 3,000 steps/day above baseline by breaking occupational sitting time, integrating incidental walking into work tasks, encouraging active transport/ lunch breaks. Maintenance phase (weeks 9–19): automated emails encouraging workers to sustain sitting reductions and step count increases sent weekly (weeks 9–12) then every 2 weeks (weeks 14-16)	8 weeks ramping, 11 weeks maintenance	varied	varied	varied	SBP DBP

Study	Country	Sample Characteristics (key descriptors, age [years, $M(SD)$], male/female [n], BMI [kg/m^2 , $M(SD)$])	Design	Intervention Details						Vascular Outcome(s)
				Total Duration	Type of PA	Duration/Frequency	Number of Bouts	Total Active Time	Estimated Total Energy Expenditure (kcal/kg)	
Wennberg et al., 2016 ⁴⁸	Australia	Inactive middle-age/older adults with overweight/obesity ($N=19$) Age: 59.7 (8.1) Male/Female: 10/9 BMI: 31.5 (4.7)	Crossover RCT	7 h	Light intensity walking (treadmill, 3.2 km/h, 0% grade)	3 min break every 30 min (after initial 2 h sedentary period)	10	30 min	1.40	SBP DBP HR
Wheeler et al., 2019a, ⁵⁰ 2019b ⁴⁹	Australia	Inactive, sedentary older adults with overweight/obesity $N=67$ (overall) ⁴⁹ Age: 67 (7) Male/Female: 32/35 BMI: 31.2 (4.1) $N=12$ (cerebral blood flow sub-study) ⁵⁰ Age: 70 (7) Male/Female: 10/2 BMI: 30.4 (4.3)	Crossover RCT	8 h	Moderate intensity walking (treadmill, 3.2 km/h, grade to achieve 65-75% of age-predicted max HR) Moderate intensity walking (continuous bout) (treadmill, 3.2 km/h, grade to achieve 65-75% of age-predicted max HR) + light intensity walking (treadmill, 3.2 km/h, 0% grade) (breaks)	30 min continuous bout 30 min continuous bout + 3 min break every 30 min	1 1 + 12	30 min 30 min + 36 min	3.36 3.36 + 1.68	SBP ⁴⁹ DBP MAP HR Epinephrine Norepinephrine MCAv ⁵⁰

Study	Country	Sample Characteristics (key descriptors, age [years, $M(SD)$], male/female [n], BMI [kg/m^2 , $M(SD)$])	Design	Intervention Details						Vascular Outcome(s)
				Total Duration	Type of PA	Duration/ Frequency	Number of Bouts	Total Active Time	Estimated Total Energy Expenditure (kcal/kg)	
Yates et al., 2020 ⁵¹	UK	Healthy white European and South Asian older adults ($N=60$) Age (median [IQR]): 70.0 (67, 75) Male/Female: 31/29 BMI (median [IQR]): 26.6 (24.9, 28.3)	Crossover RCT	7.5 h	Standing	5 min break every 30 min	12	60 min	1.30	SBP
					Light intensity walking (over flat ground, self-selected pace [2.4-4.4 km/h])	5 min break every 30 min	12	60 min	3.50	
Zeigler et al., 2016 ⁵²	US	Inactive adults with overweight/obesity and prehypertension and/or impaired fasting glucose ($N=9$) Age: 30 (15) Male/Female: 2/7 BMI: 28.7 (2.7)	Crossover RCT	8 h	Standing	Progressively longer intervals 10, 15, 20, and 30 min about every hour	8	25 min	0.54	SBP DBP HR
					Light intensity walking (treadmill desk, 1.6 km/h, 0% grade)	Progressively longer intervals 10, 15, 20, and 30 min about every hour	8	25 min	0.96	
					Cycling (under desk ergometer, work rate [approximately 20 watts] and cadence to match walking condition)	Progressively longer intervals 10, 15, 20, and 30 min about every hour	8	25 min	1.46	

* adequately powered for outcome (based on power analysis and recruited sample size)
All crossover RCTs included an uninterrupted sitting group of matched length
Age and BMI reported as $M(SD)$ unless otherwise noted

BMI, body mass index; BP, blood pressure; CVC, cerebrovascular conductance; CVR, cerebrovascular CO₂ reactivity; DBP, diastolic blood pressure; FMD, flow mediated dilation; HR, heart rate; ICAM-1, intracellular adhesion molecule-1; IQR, interquartile range; MAP, mean arterial pressure; MCAv, middle cerebral artery blood flow velocity; PA, physical activity; PWV, pulse wave velocity; RCT, randomized controlled trial; SD, standard deviation; SFA, superficial femoral artery; SBP, systolic blood pressure; T2D, type 2 diabetes; UK, United Kingdom; US, United States; VCAM-1, vascular cell adhesion molecule-1

Table 2. Acute effects of different break types on systemic vascular outcomes (e.g., SBP, DBP, MAP, HR).

Outcome	Author, Year	Break Type (duration/frequency)	Effect
SBP			
	Bailey et al., 2015 ³³	Standing (2 min every 20 min)	-
	Kerr et al., 2017 ⁴³	Standing (2 min every 20 min)	-
	Kerr et al., 2017 ⁴³	Standing (10 min every 60 min)	-
	Kruse et al., 2018 ⁴⁵	Standing (10 min every 60 min)	-
	Yates et al., 2020 ⁵¹	Standing (5 min every 30 min)	-
	Barone Gibbs et al., 2017 ³⁴	Standing (30 min every 30 min)	-
	Zeigler et al., 2016 ⁵²	Standing (variable, 10-30 min about every 60 min)	↓
	Kerr et al., 2017 ⁴³	Light walking (2 min every 60 min)	-
	Bailey et al., 2015 ³³	Light walking (2 min every 20 min)	-
	Wennberg et al., 2016 ⁴⁸	Light walking (3 min every 30 min)	-
	Freire et al., 2019 ⁴²	Light walking (5 min every 20 min)	-
	Zeigler et al., 2016 ⁵²	Light walking (variable, 10-30 min about every 60 min)	↓
	Larsen et al., 2014 ⁴⁶	Light walking (2 min every 20 min)	↓↓
	Dempsey et al., 2016 ⁴¹	Light walking (3 min every 30 min)	↓↓
	Yates et al., 2020 ⁵¹	Light walking (5 min every 30 min)	↓↓
	Champion et al., 2018 ³⁹	Light walking (20 min every 60 min)	↓↓
	Kruse et al., 2018 ⁴⁵	Light intensity desk pedaling (10 min every 60 min)	-
	Zeigler et al., 2016 ⁵²	Cycling (variable, 10-30 min about every 60 min)	↓
	Bhammar et al., 2017 ³⁶	Moderate walking (2 min every 20 min)	-
	Larsen et al., 2014 ⁴⁶	Moderate walking (2 min every 20 min)	↓
	Wheeler et al., 2019b ⁴⁹	Moderate walking (30 min continuous bout + 3 min every 30 min)	↓↓
	Bhammar et al., 2017 ³⁶	Vigorous walking (2 min every 60 min)	-
	Kowalsky et al., 2019 ⁴⁴	Resistance exercises (variable, 1.3-2.6 min every 60 min)	-
	Climie et al., 2018 ⁴⁰	Resistance exercises (3 min every 30 min)	-
	Dempsey et al., 2016 ⁴¹	Resistance exercises (3 min every 30 min)	↓↓
	Puig-Ribera et al., 2015 ⁴⁷	Community-based intervention	-
DBP			
	Bailey et al., 2015 ³³	Standing (2 min every 20 min)	-
	Kerr et al., 2017 ⁴³	Standing (2 min every 20 min)	-
	Kerr et al., 2017 ⁴³	Standing (10 min every 60 min)	-
	Kruse et al., 2018 ⁴⁵	Standing (10 min every 60 min)	-
	Barone Gibbs et al., 2017 ³⁴	Standing (30 min every 30 min)	↓
	Zeigler et al., 2016 ⁵²	Standing (variable, 10-30 min about every 60 min)	↑
	Bailey et al., 2015 ³³	Light walking (2 min every 20 min)	-
	Wennberg et al., 2016 ⁴⁸	Light walking (3 min every 30 min)	-
	Zeigler et al., 2016 ⁵²	Light walking (variable, 10-30 min about every 60 min)	-
	Kerr et al., 2017 ⁴³	Light walking (2 min every 60 min)	↑+
	Champion et al., 2018 ³⁹	Light walking (20 min every 60 min)	↓
	Freire et al., 2019 ⁴²	Light walking (5 min every 20 min)	↓
	Larsen et al., 2014 ⁴⁶	Light walking (2 min every 20 min)	↓↓
	Dempsey et al., 2016 ⁴¹	Light walking (3 min every 30 min)	↓↓
	Kruse et al., 2018 ⁴⁵	Light intensity desk pedaling (10 min every 60 min)	-
	Bhammar et al., 2017 ³⁶	Moderate walking (2 min every 20 min)	-
	Larsen et al., 2014 ⁴⁶	Moderate walking (2 min every 20 min)	↓
	Wheeler et al., 2019b ⁴⁹	Moderate walking (30 min continuous bout + 3 min every 30 min)	↓↓
	Zeigler et al., 2016 ⁵²	Cycling (variable, 10-30 min about every 60 min)	↓
	Bhammar et al., 2017 ³⁶	Vigorous walking (2 min every 60 min)	-
	Kowalsky et al., 2019 ⁴⁴	Resistance exercises (variable, 1.3-2.6 min every 60 min)	-

Outcome	Author, Year	Break Type (duration/frequency)	Effect
	Climie et al., 2018 ⁴⁰	Resistance exercises (3 min every 30 min)	↑*
	Dempsey et al., 2016 ⁴¹	Resistance exercises (3 min every 30 min)	↓↓
	Puig-Ribera et al., 2015 ⁴⁷	Community-based intervention	-
MAP			
	Barone Gibbs et al., 2017 ³⁴	Standing (30 min every 30 min)	↓
	Carter et al., 2019 ³⁸	Light walking (2 min every 30 min)	-
	Carter et al., 2019 ³⁸	Light walking (8 min every 120 min)	-
	Larsen et al., 2014 ⁴⁶	Light walking (2 min every 20 min)	-
	Champion et al., 2018 ³⁹	Light walking (20 min every 60 min)	↓
	Freire et al., 2019 ⁴²	Light walking (5 min every 20 min)	↓*
	Larsen et al., 2014 ⁴⁶	Moderate walking (2 min every 20 min)	-
	Bhammar et al., 2017 ³⁶	Moderate walking (2 min every 20 min)	-
	Wheeler et al., 2019b ⁴⁹	Moderate walking (30 min continuous bout + 3 min every 30 min)	↓↓
	Bhammar et al., 2017 ³⁶	Vigorous walking (2 min every 60 min)	-
HR			
	Kerr et al., 2017 ⁴³	Standing (2 min every 20 min)	-
	Kerr et al., 2017 ⁴³	Standing (10 min every 60 min)	-
	Kruse et al., 2018 ⁴⁵	Standing (10 min every 60 min)	-
	Zeigler et al., 2016 ⁵²	Standing (variable, 10-30 min about every 60 min)	-
	Barone Gibbs et al., 2017 ³⁴	Standing (30 min every 30 min)	↑*
	Carter et al., 2019 ³⁸	Light walking (2 min every 30 min)	-
	Carter et al., 2019 ³⁸	Light walking (8 min every 120 min)	-
	Kerr et al., 2017 ⁴³	Light walking (2 min every 60 min)	-
	Larsen et al., 2014 ⁴⁶	Light walking (2 min every 20 min)	-
	Dempsey et al., 2016 ⁴¹	Light walking (3 min every 30 min)	↓
	Wennberg et al., 2016 ⁴⁸	Light walking (3 min every 30 min)	↑
	Zeigler et al., 2016 ⁵²	Light walking (variable, 10-30 min about every 60 min)	↑
	Kruse et al., 2018 ⁴⁵	Light intensity desk pedaling (10 min every 60 min)	-
	Zeigler et al., 2016 ⁵²	Cycling (variable, 10-30 min about every 60 min)	↑
	Larsen et al., 2014 ⁴⁶	Moderate walking (2 min every 20 min)	-
	Wheeler et al., 2019b ⁴⁹	Moderate walking (30 min continuous bout + 3 min every 30 min)	↑↑
	Dempsey et al., 2016 ⁴¹	Resistance exercises (3 min every 30 min)	-
	Climie et al., 2018 ⁴⁰	Resistance exercises (3 min every 30 min)	↑↑
	Kowalsky et al., 2019 ⁴⁴	Resistance exercises (variable, 1.3-2.6 min every 60 min)	↑↑

Note: - No effect; ↑ Single arrow $p < 0.05$; ↑↑ Double arrow $p < 0.01$; ↑* Trend - $p 0.05-0.1$; ↑⁺ $p 0.0167-0.05$ where $p < 0.0167$ considered statistically significant based on reported Bonferroni adjustment.

Direction of observed effect is reflected in directionality of arrow. Prolonged sitting is the reference condition in all except Puig-Ribera et al., 2015,⁴⁷ in which the reference group was an attention-control group.

DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure

Table 3. Acute effects of different break types on regional vascular outcomes (e.g., PWV, superficial femoral artery FMD, cerebral blood flow).

Outcome	Author, Year	Break Type (duration/frequency)	Effect
PWV – Carotid-Femoral			
	Barone Gibbs et al., 2017 ³⁴	Standing (30 min every 30 min)	-
	Kowalsky et al., 2019 ⁴⁴	Resistance exercises (variable, 1.3-2.6 min every 60 min)	-
PWV – Carotid-Ankle			
	Barone Gibbs et al., 2017 ³⁴	Standing (30 min every 30 min)	↓
	Kowalsky et al., 2019 ⁴⁴	Resistance exercises (variable, 1.3-2.6 min every 60 min)	-
PWV – Carotid-Radial			
	Barone Gibbs et al., 2017 ³⁴	Standing (30 min every 30 min)	-
	Kowalsky et al., 2019 ⁴⁴	Resistance exercises (variable, 1.3-2.6 min every 60 min)	-
SFA FMD			
	Carter et al., 2019 ³⁸	Light walking (2 min every 30 min)	-
	Carter et al., 2019 ³⁸	Light walking (8 min every 120 min)	-
	Climie et al., 2018 ⁴⁰	Resistance exercises (3 min every 30 min)	↑↑
	Kerr et al., 2017 ⁴³	Standing (2 min every 20 min)	-
	Kerr et al., 2017 ⁴³	Standing (10 min every 60 min)	↑+
	Kerr et al., 2017 ⁴³	Light walking (2 min every 60 min)	↑↑
SFA blood flow			
	Carter et al., 2019 ³⁸	Light walking (2 min every 30 min)	-
	Carter et al., 2019 ³⁸	Light walking (8 min every 120 min)	↑
	Climie et al., 2018 ⁴⁰	Resistance exercises (3 min every 30 min)	-
SFA shear rate			
	Carter et al., 2019 ³⁸	Light walking (2 min every 30 min)	-
	Carter et al., 2019 ³⁸	Light walking (8 min every 120 min)	↑*
	Climie et al., 2018 ⁴⁰	Resistance exercises (3 min every 30 min)	-
MCAv			
	Perdomo et al., 2019 ³⁵	Standing (30 min every 30 min)	-
	Carter et al., 2018 ³⁷	Light walking (2 min every 30 min)	↑
	Carter et al., 2018 ³⁷	Light walking (8 min every 120 min)	-
	Wheeler et al., 2019a ⁵⁰	Moderate walking (30 min continuous bout + 3 min every 30 min)	-

Note: - No effect; ↑ Single arrow $p < 0.05$; ↑↑ Double arrow $p < 0.01$; ↑* Trend - $p 0.05-0.1$; ↑+ $p 0.0167-0.05$ where $p < 0.0167$ considered statistically significant based on reported Bonferroni adjustment.

Direction of observed effect is reflected in directionality of arrow. Prolonged sitting is the reference condition.

FMD, flow mediated dilation; MCAv, middle cerebral artery blood flow velocity; PWV, pulse wave velocity; SFA, superficial femoral artery

Table 4. Summary of key eligibility and methodological issues associated with rigor that were addressed and reported in the included studies.

Author, Year	Eligibility					Study Visits					
	Objective Measurement of SB/PA (prior to)	Documentation of DM Status (via HbA1c)	Menopausal Status	Washout Period (≥ 7 d)	Female Hormonal Cycle	Diet Standardization	Abstention from MVPA (≥ 48 h)	Abstention from Alcohol/Caffeine (≥ 24 h)	Abstention from Tobacco/Smoking	Sex Balance (40-60%)	Objective Measurement of SB/PA (during)
Bailey et al., 2015 ³³	-	N/A	-	- (≥ 6 d)	-	+ (during only)	- (24 h)	+	-	- (30% female)	-
Barone Gibbs et al., 2017, ³⁴ Perdomo et al., 2019 ³⁵	-	N/A	-	- (5-14 d)	-	+ (during only)	- (24 h)	- (24 h caffeine, 12 h alcohol)	+	- (36% female)	+
Bhammar et al., 2017 ³⁶	-	N/A	+ (post excluded)	- (≥ 72 h, avg duration 7 d)	+	+ (during and before)	-	-	+	+	+
Carter et al., 2018, ³⁷ 2019 ³⁸	-	N/A	-	- (all visits in 17 d period)	+	+ (during only)	- (24 h)	- (overnight)	+	- (33% female)	-
Champion et al., 2018 ³⁹	-	N/A	-	- (≥ 6 d)	+	+ (before and during)	+	+	+	+	+
Climie et al., 2018 ⁴⁰	-	+ (excluded by HbA1c)	+ (pre excluded)	- (≥ 6 d)	N/A	+ (before and during)	+	+	+	+	-
Dempsey et al., 2016 ⁴¹	-	+	-	- (6-14 d)	-	+ (during only)	+	+	-	+	-
Freire et al., 2019 ⁴²	+	N/A	+	+	-	+ (during only)	- (24 h)	+	+	+	+
Kerr et al., 2017 ⁴³	-	+	+	+	N/A	+ (before and	+	- (alcohol 48	+	- (100%	-

Author, Year	Eligibility			Study Visits							
	Objective Measurement of SB/PA (prior to)	Documentation of DM Status (via HbA1c)	Menopausal Status	Washout Period (≥ 7 d)	Female Hormonal Cycle	Diet Standardization	Abstinence from MVPA (≥ 48 h)	Abstinence from Alcohol/Caffeine (≥ 24 h)	Abstinence from Tobacco/Smoking	Sex Balance (40-60%)	Objective Measurement of SB/PA (during)
		excluded)	excluded)			during)		h, caffeine not reported)	excluded)	female)	
Kowalsky et al., 2019 ⁴⁴	-	-	-	- (2-14 d)	+	+	- (12 h)	- (alcohol 24 h, caffeine 12 h)	+	- (86% female)	-
Kruse et al., 2018 ⁴⁵	-	-	- (“considered ” peri)	- (48 h)	+	+	+	+	+	- (23% female)	-
Larsen et al., 2014 ⁴⁶	-	-	-	+	-	+	+	+	+	+	-
Puig-Ribera et al., 2015 ⁴⁷	-	-	-	N/A	-	-	-	-	-	- (64% female)	+
Wennberg et al., 2016 ⁴⁸	+	-	-	- (6 d)	-	+	+	-	+	+	+
Wheeler et al., 2019a, ⁴⁹ 2019b ⁵⁰	-	-	+	- (≥ 6 d)	-	+	+	+	-	+ ⁴⁹	-
Yates et al., 2020 ⁵¹	+	-	-	+	-	+	+	-	-	+	+
	(activPAL and Geneactiv)		(age 65+)			(before and during)		(alcohol 48 h, caffeine not reported)			(Geneactiv)
Zeigler et al., 2016 ⁵²	+	-	-	+	-	+	- (24 h)	-	-	- (78% female)	+
	(Geneactiv)					(before and during)					(activPAL and Geneactiv)

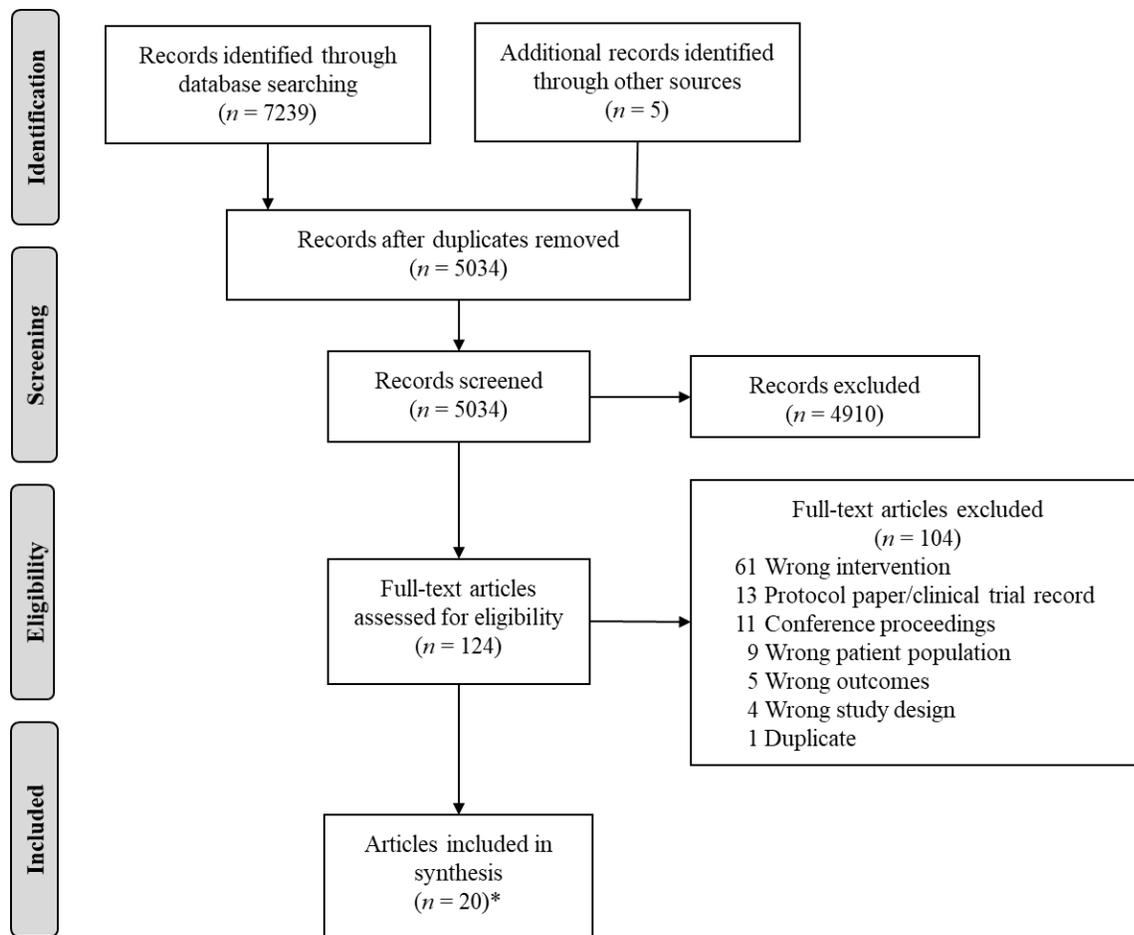
Note: N/A not applicable; +Criteria met and/or adequately explained; - Criteria not met or adequately explained

DM, diabetes mellitus; HbA1c, hemoglobin A1c; MVPA, moderate to vigorous physical activity; PA, physical activity; SB, sedentary behavior

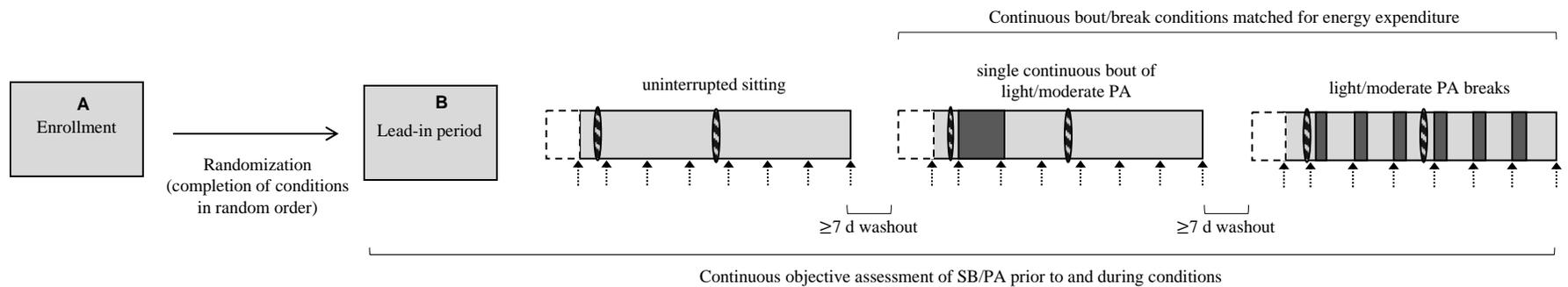
FIGURE LEGENDS

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 2. Schematic of theoretical study design to examine the effects of sedentary breaks on vascular outcomes in humans with key design characteristics we recommend researchers consider.



*representing 17 unique studies



A:

- Adequate sample size (power) to detect changes in vascular outcome(s) and examine sex differences
- Verification of T2D status (via HbA1c, fasting glucose), hypertension (rigorously measured BP), and menopausal status (via FSH)
- Objective assessment of SB/PA patterns

B:

- All conditions conducted during follicular phase of female hormonal cycle
- Diet standardization (via controlled diet or documentation and replication of dietary intake) evening prior to each condition
- Familiarization to study procedures (outcome assessment and breaks)
- Abstain from MVPA ≥ 48 h
- Abstain from caffeine/alcohol ≥ 24 h
- Abstain from tobacco/smoking ≥ 12 h



Standard meal/snack



Vascular measurement (both systemic as well as regional/hormonal outcomes) completed before exercise/breaks and at regular intervals



PA (compare multiple types including light and moderate ambulatory activity, resistance training, seated cycling, etc.)



Steady state period prior to data collection in each condition

BP: blood pressure; FSH, follicle stimulating hormone; HbA1c, hemoglobin A1c; MVPA, moderate to vigorous physical activity; PA, physical activity; SB, sedentary behavior; T2D, type 2 diabetes