Scandinavian Journal of Medicine & Science in Sports

WILEY

REVIEW

Optimal Frequency of Interrupting Prolonged Sitting for Cardiometabolic Health: A Systematic Review and Meta-Analysis of Randomized Crossover Trials

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Received: 13 July 2024 | **Revised:** 28 August 2024 | **Accepted:** 11 November 2024

Funding: The authors received no specific funding for this work.

Keywords: cardiometabolic health | exercise snacks | glucose control | interrupting prolonged sitting | meta-analysis | prolonged sitting | sedentary behavior | sedentary breaks

ABSTRACT

Increasing evidence highlights the efficacy of interruptions in prolonged sitting (i.e., activity/sedentary breaks) for improving cardiometabolic health, but precise conclusions and recommendations regarding the optimal interruption frequency remain poorly defined. This systematic review and meta-analysis aimed to directly compare the effect of different frequencies of interrupting prolonged sitting on cardiometabolic health and to determine potential moderators. Randomized crossover trials with at least two frequency interruptions compared to a prolonged sitting condition were identified via systematic review. We compared the acute effects of high-frequency (≤ 30 min per bout, HF) versus low-frequency (> 30 min per bout, LF) interruption protocols on various cardiometabolic health outcomes via three-level meta-analysis with pooled effects evaluated within a random-effects model and exploration of potential sources of heterogeneity through subgroup analyses. The quality of evidence was assessed using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Thirteen studies with 211 participants (24–66 years, 41% female) were included. When comparing HF to LF condition, the HF had a significantly greater reduction in glucose (9 studies [$n = 740$]; Hedge's $g = -0.30$, 95% CI [−0.57, −0.03], $p = 0.03$; I^2-level 3 = 42%, PI [−1.01, 0.41]). However, there was no difference in insulin (4 studies [$n = 304$]; Hedge's $g = -0.22$, 95% CI [−0.73, 0.29], $p = 0.35$; I^2-level 3 = 52%, PI [−1.18, 0.74]), triglyceride (3 studies [$n = 484$]; Hedge's $g = 0.11$, 95% CI [−0.10, 0.30], $p = 0.29$; I^2-level 3 = 0%, PI [−0.10, 0.30]), blood pressure (5 studies [$n = 352$]; Hedge's $g = -0.06$, 95% CI [−0.41, 0.28], $p = 0.69$; I^2-level 3 = 35%, PI [−0.81, 0.62]), and superficial femoral flow-mediated dilation (3 studies [$n = 98$]; Hedge's $g = -0.42$, 95% CI [−2.43, 1.60], $p = 0.47$; I^2-level 3 = 78%, PI [−4.09, 3.25]) between the two conditions. The quality of evidence was low GRADE for all outcomes. The present study suggests that a higher sedentary interruption frequency might be more efficacious than a lower frequency/higher duration protocol for reducing glucose levels. Based on these findings, interrupting sedentary time at least, every 30 min may be an ideal strategy to improve glucose control.

1 | Introduction

Technological advances have led to increasingly sedentary lifestyles in developed countries [1]. Sedentary behavior, defined as any waking behaviors that require low levels of energy expenditure (< 1.5 METS) while in a sitting, reclining, or lying posture [2], is associated with a greater risk for several chronic diseases [3, 4], including Type 2 diabetes (T2D) mellitus and cardiovascular disease [5]. Strong dose–response associations have also been reported between prolonged sedentary behavior and risk of all-cause and cardiovascular disease-related mortality [5]. The accumulation of epidemiological evidence linking excessive sedentary behavior to adverse health outcomes has prompted revisions to physical activity guidelines. For example, the second edition of the Physical Activity Guidelines for Americans, for the first time, acknowledged that individuals could derive health benefits from reducing sedentary time and recommended that all adults should sit less and move more [6]. Similarly, the World Health Organization (WHO) has expanded its physical activity guidelines and recommends the reduction of sedentary time in addition to engaging in regular moderate-vigorous physical activity [7].

Evolutionary, exposure to sedentary behavior is likely not a new phenomenon. However, the current societal and cultural environment has evolved in a way that promotes (and/or necessitates) long-duration bouts of uninterrupted sitting [8]. Fortunately, randomized crossover trials have substantiated that interrupting prolonged sitting throughout the day with various modes of activity or standing (i.e., activity/sedentary breaks) elicits a favorable effect on cardiometabolic health [3, 4]. Thus, it is purported that the potential harm associated with prolonged sedentary behavior, including detrimental effects on glucose metabolism [9–12] and vascular function [13–18], can be mitigated with regular sedentary breaks. Moreover, evidence suggests [19] that interrupting prolonged sedentary behavior throughout the day may be superior in regulating glucose levels than a single session of exercise [11, 20]. Thus, sedentary breaks, regardless of the modality, may be a viable public health strategy to offset the harms of prolonged sedentary behavior.

Although numerous systematic reviews have summarized the effect of sedentary breaks/interruptions on cardiometabolic health [9–16], the optimal dose of breaks/interruptions on cardiometabolic health in terms of frequency has largely not been elucidated among existing systematic reviews. Such information is necessary to provide the public with more specific recommendations to mitigate the harms of sedentary behavior beyond "sit less and move more." Research is especially needed to delineate the optimal frequency of sedentary breaks. Among adults with T2D, a sedentary break that consisted of simple resistance exercises at a frequency/duration dose of every 60 min for 6 min (low frequency, high duration) was efficacious in reducing glucose and insulin compared to prolonged sitting, but no effects were observed at a frequency/duration dose of every 30 min for 3 min (high frequency, low duration) [21]. In contrast, Wongpipit et al. [22] observed that high-frequency low-duration sedentary breaks consisting of light-intensity walking every 30 min for 3 min were superior to low-frequency high-duration breaks (every 60 min for 6 min) in reducing glucose among obese adults. The divergent outcomes observed across studies may be potentially attributable to variations in study design elements or participant characteristics and has led to conflicting assertions regarding the optimal break frequency [23]. The inconsistency of findings underscores the need for arbitration through a comprehensive review and synthesis of the existing evidence.

Current guidelines on sedentary behavior lack specificity in providing recommendations on key details, such as thresholds/targets for the frequency of sedentary breaks [6, 7, 24]. It remains uncertain whether a strategy emphasizing high or low frequency is preferable in practical applications. The most recent edition of the Standards of Medical Care in Diabetes from the American Diabetes Association recommends that "prolonged sitting should be interrupted every 30 minutes for blood glucose benefits" [25]. However, it is crucial to note that this recommendation is based on a crossover trial conducted by Dempsey et al. [26], which did not compare various frequencies (e.g., 30 min vs. 60 min per bout) of sedentary breaks "head-to-head." It is unclear if this recommendation (breaks every 30 min) represents the optimal glucose management frequency of interrupting sedentary time.

Consequently, a comprehensive systematic review and meta-analysis are imperative to establish a higher level of evidence [27], serving to reconcile disparate findings and furnish the requisite evidence for future updates to guidelines on optimal strategies for interrupting sedentary behavior. Additionally, a meta-analysis can address questions that individual trials cannot, such as identifying the key sources of heterogeneity in findings (e.g., participant characteristics, interrupting protocol, and study design). Given that the optimal frequency of interruptions is likely not a "one size fits all" approach [28]—for example, the optimal frequency to improve glycemic control in T2D may be different from that needed to regulate blood pressure in patients with hypertension—there is methodological value to and need for conducting a meta-analysis of the existing evidence base.

Therefore, this study aims to conduct a systematic review of the acute effect of varying frequency of interrupting prolonged sitting on cardiometabolic health among randomized crossover trials. We specifically aimed to evaluate the following questions.

1. Pre there differences in the efficacy of sedentary interruptions with high frequency (≤ 30 min per bout, HF) versus low frequency (> 30 min per bout, LF) on indicators of cardiometabolic health, including glucose and lipid metabolism, blood pressure, and vascular function, among adults with or without any health condition?
2. Are the differences in effects of HF and LF moderated by participants' characteristics (e.g., glucose status), interrupting protocol (e.g., mode), and study design (e.g., equivalent duration)?

2 | Methods

The reporting of this systematic review follows the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [29]. The completed PRISMA

2020 checklist can be found in Appendix S1. This review was registered in the PROSPERO database (CRD42024509778).

2.1 | Information Sources

PubMed (NCBI), Web of Science (Core Collection), and Cochrane Library (Embase, CT.gov, and ICTRP) were searched from database inception to January 2024. To be included in this review, studies must be full-text, peer-reviewed articles written in English. No date or sample restrictions were implemented in the search portion of this review.

2.2 | Search Strategy

Considering that some of the studies did not explicitly mention frequency of sedentary breaks in the title and keywords, a more comprehensive search strategy was used to identify studies examining the effects of sedentary interruptions on cardiometabolic health as fully as possible. Using the Web of Science as an example, we searched for the following terms by title, abstract, and keywords: TS = (sedentary OR sitting) AND TS = (cardiometabolic OR cardio OR vascular OR cardiovascular) AND TS = (older adults OR adults OR individuals) AND TS = (break* OR interrupt* OR fraction* OR intersperse* NOT ejection fraction). This search strategy is similar to those used in a recently published systematic review [12]. We applied three systematic snowballing searches: (1) screened the reference list of included articles; (2) screened articles that cited the included articles; (3) conducted related articles searches for each included article (MEDLINE and Embase). We also screened articles identified in previous systematic reviews on the effects of sedentary breaks on health outcomes. 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.

2.3 | Selection Process

De-duplication of retrieved records was done manually by an independent reviewer using EndNote X9 [Clarivate Analytics, 2018]. Subsequently, the deduplicated records were exported and screened by two independent researchers. Records were screened according to predefined inclusion and exclusion criteria, screening the titles and abstracts of all articles. In case of discrepancies, a meeting was convened between the two researchers to reach a consensus through a review of the inclusion criteria and subsequent discussion. In situations where consensus was not reached, a third independent researcher was included to achieve consensus. Next, the two independent researchers conducted a comprehensive review of the full texts to identify the final studies for inclusion. In cases of discrepancies, the same protocol employed during the title and abstract screening phase was implemented.

2.4 | Eligibility Criteria

A priori inclusion and exclusion criteria were used to evaluate study eligibility under the PICOS framework. Only studies among adults (age 18+) with or without any health condition were included. Animal studies were excluded during the title/abstract screening phase. Only studies where (1) a crossover experimental trials under laboratory conditions was conducted that included an uninterrupted sitting condition and sedentary interruption conditions, (2) prolonged sitting was interrupted with multiple physical activity bouts or standing spread throughout the sedentary interruption condition, (3) there was clear information on the interruption protocol, (4) included ≥ 2 doses of differing frequencies, and (5) assessed at least one cardiovascular or metabolic outcome reflective of glucose metabolism (fasting or postprandial blood glucose/insulin, or other outcomes related to glucose, insulin such as glycated hemoglobin, duration of hyperglycemia, and glycemic variability), lipid metabolism (fasting or postprandial triglyceride), blood pressure, or vascular function (blood flow, shear rate, flow-mediated vascular dilation, and cerebral blood flow) were included. Studies were excluded if the following conditions were met: (1) the trial lacked a washout period; (2) there were uncontrolled rest periods outside the specified intervention time. Qualitative studies, trials/interventions conducted in free-living settings, systematic reviews/meta-analyses, study protocols, gray literature, and published abstracts were excluded from this review.

2.5 | Data Extraction

Data extraction was conducted by the two reviewers responsible for the screening phase, utilizing a customized extraction worksheet in Excel finalized prior to full-text screening. The two reviewers independently extracted the following information: author and study details, participant information, sedentary and interruption protocols, and outcomes related to cardiovascular/metabolic health. A third independent researcher resolved any discrepancies. If data were missing or only presented graphically, authors were contacted to request the necessary information [30]. If this contact attempt was unsuccessful, and the data were available only in graphical form, relevant data (Kerr et al. [31]) were extracted using WebPlotDigitizer 4.1 (https://automeris.io/WebPlotDigitizer). This software has been demonstrated to have high reliability and validity [32]. If we were unable to successfully obtain missing information, the specific study was excluded from the analysis.

2.6 | Data Conversion

We extracted the mean, standard deviations (SD), and sample size reported for each condition and outcome. If the study only reported confidence intervals, they were converted to SD using the following formula [27]:

$$\mathrm{SD} = \sqrt{N}\,\frac{\mathrm{CI}_{\mathrm{high}} - \mathrm{CI}_{\mathrm{low}}}{2t}$$

where SD is the standard deviation, N is the group sample size, $\mathrm{CI}_{\mathrm{high}}$ is the upper limit of the confidence interval, $\mathrm{CI}_{\mathrm{low}}$ is the lower limit of the confidence interval, and t is the t distribution with $N-1°$ of freedom the respective confidence level [27].

If the study only reported standard errors (SE), they were converted to SD using the following formula [27]:

$$SD = \sqrt{N} \times SE$$

2.7 | Risk of Bias and Methodological Quality

The risk of bias was assessed independently by two reviewers, with disagreements resolved via discussion if possible, and, if not, arbitrated by a third researcher, using the Cochrane Collaboration's Risk of Bias tool 2 (ROB 2) [33]. This tool evaluates five areas: random sequence generation, random allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

Moreover, an assessment of key methodological design elements within the field of experimental sedentary behavior trials was also conducted [34]. Relevant elements included achieving sex balance, controlling for menstrual cycles, objectively quantifying physical activity and sedentary behavior using accelerometers before and during the trial, prohibiting moderate-to-vigorous physical activity before the trial, implementing washout periods, restricting alcohol, caffeine, and smoking before the trial, and standardizing dietary conditions.

2.8 | Statistical Analysis

2.8.1 | Three-Level Meta-Analysis

Studies on interrupting prolonged sitting typically report multiple measures, such as the incremental area under the curve (iAUC), the total area under the curve (tAUC), and mean glucose levels [11], along with comparisons of varying frequencies within a single study [30]. In such studies, different effect sizes are often correlated, and including them simultaneously can violate the assumption of independence in traditional meta-analyses [35]. Conversely, considering only one effect size or outcome measure might be too conservative [11], failing to accurately reflect the true effect [36]. To address this, we utilized a three-level meta-analysis following the methods by Assink and Wibbelink [37], with the analysis performed using open-source R code [38]. Multiple measurements and comparisons within the same study were nested, allowing the variance of observed effect sizes to be decomposed into sampling variance, within-study variance (Level 2), and between-study variance (Level 3), thus accounting for within-study (or within-group) correlations [39]. Three-level meta-analyses approach acknowledges the hierarchical structure of the data (e.g., effect sizes nested within studies), preserving valuable information from multiple effects within each study, thereby enhancing statistical power and providing a more realistic representation of effect sizes [37].

Three-level meta-analyses were conducted using the metafor packages in the statistical software R (V.4.2.0) [40]. Means and SD were extracted from individual studies to calculate Hedge's *g* for each study and were classified as trivial (0.2), small (0.2–0.5), medium (0.5–0.8), and large (>0.8) [41]. The inverse of the standard error was used to determine the weight (i.e., contribution) of each effect (i.e., correlation coefficient) in the meta-analysis [42]. The model parameters were estimated using the restricted maximum likelihood (REML) method, and the calculations were cross-verified with the maximum likelihood (ML) method to ensure result stability. Tests of individual coefficients in all models, and their corresponding confidence intervals (CI), were based on a t-distribution [38]. Additionally, the statistical power of the primary pooled effect was calculated, and the possibility of false-negatives due to insufficient statistical power was considered. Statistical power was calculated using the *metameta* package [43].

Given that the prediction interval (PI) is a measure of the effect of the treatment considering heterogeneity and can provide useful additional information for the CI especially when using a random-effects model [44, 45], the PI was additionally calculated based on t-distribution [46]. Numerous variables are commonly used to assess heterogeneity (Cochrane's Q, I^2 statistic, tau^2, and Tau) [47], but most of the available literature supports the use of I^2 statistic (I^2) as the primary source of information on the degree of heterogeneity. Therefore, the main analysis reports I^2 with the following interpretations: <25%, 25%–75%, and >75% representing low, moderate, and considerable impact of heterogeneity, respectively [48].

2.8.2 | Subgroup Analysis

To investigate the sources of heterogeneity between studies and moderating factors, the following variables were included in subgroup analyses: (1) glucose status (normal glucose [sample mean fasting glucose <100 mg/dL, if the authors did not report anything about the participant's glucose status it was considered normal glucose], impaired glucose [fasting glucose level ≥100 ~ 125 mg/dL or diagnosed diabetes glucose]); (2) sex (mixed, male only, female only); (3) age (<60 years, ≥60 years); (4) weight status (non-obese [BMI <30 kg·m^{-2}]), obese [BMI >30 kg·m^{-2}], (5) mode of sedentary breaks; and (6) total duration of sedentary breaks. The statistical power of each subgroup was calculated to inform the possibility of false-negatives due to insufficient statistical power [43].

2.8.3 | Publication Bias and Sensitivity Analysis

The contour-enhanced funnel plot [49], in conjunction with Egger's asymmetry test [50] was employed to assess publication bias (tests were only conducted when $k \geq 10$ [51]), and the $p > 0.05$ was considered without risk of publication bias. Funnel plots and Egger's regression tests are primarily used to determine the symmetry of the overall effect size, either through subjective or quantitative measures, thereby assessing the risk of publication bias in the included studies.

Sensitivity analyses were performed by comparing a three-level meta-analysis with the traditional two-level meta-analysis. The traditional meta-analysis utilized a generic inverse-variance pooling method, with effect sizes (only use iAUC [11]) pooled using a random-effects model based on the DerSimonian and Laird approach [52]. For studies with multiple interruption conditions (e.g., standing and walking) or doses, the sample size was adjusted by dividing it by the number of conditions, following Cochran's guidelines, to mitigate bias due to sample size inflation [27]. Post hoc model analysis confirmed that the three-level model provided a significantly better fit compared to the two-level model, in which Level 3 heterogeneity was constrained to zero. Additionally, a sequential exclusion of one trial at a time

was conducted to evaluate the robustness of the pooled results in the two-level meta-analysis.

In the three-level meta-analysis, Hat [53], Cook's distance [53], and studentized residuals [54] were employed to diagnose leverage, outliers, and influential cases at the within-study level (Level 2) and between-study level (Level 3), respectively. Cases were flagged if their Hat and Cook's distance values exceeded three times their respective means, or if their studentized residuals had absolute values greater than 3. The three-level meta-analysis was then repeated after excluding these outliers to assess the model's stability.

2.9 | Certainty of the Evidence

Evidence of effectiveness for each study was combined with quality scores for use in discussing the results. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to rate the certainty of the evidence as "high," "moderate," "low," or "very low" [55]. GRADE was completed by two researchers, with differences resolved through consensus.

This comprehensive assessment rates evidence as follows: (1) the risk of bias, downgraded by one level if "some concerns" and two levels if "high risk" of bias; (2) inconsistency, downgraded by one level when the impact of statistical heterogeneity (I^2) is moderate (> 25%) and by two levels when high > 75%; (3) imprecision: downgraded by one level when statistical power < 80% and if there was no clear direction of the effects [56]; (4) risk of publication bias: downgrade one level if Egger's test < 0.05.

3 | Results

3.1 | Search Results

We systematically searched five databases and the initial search yielded 926 publications. We screened the full text of 75 papers. Out of these, 13 papers were included in this systematic review and meta-analysis (Figure 1).

3.2 | Characteristics of Included Studies

The included studies (13 articles) comprised a total of 211 participants (female = 86, 41%), and sample sizes ranged from 10 to 24, with mean ages from 24 to 66 years. The populations studied included apparently healthy ($n = 5$ studies) [20, 57–61], obese ($n = 8$ studies) [21–23, 30, 31, 62–64], prediabetic ($n = 1$ studies) [62],

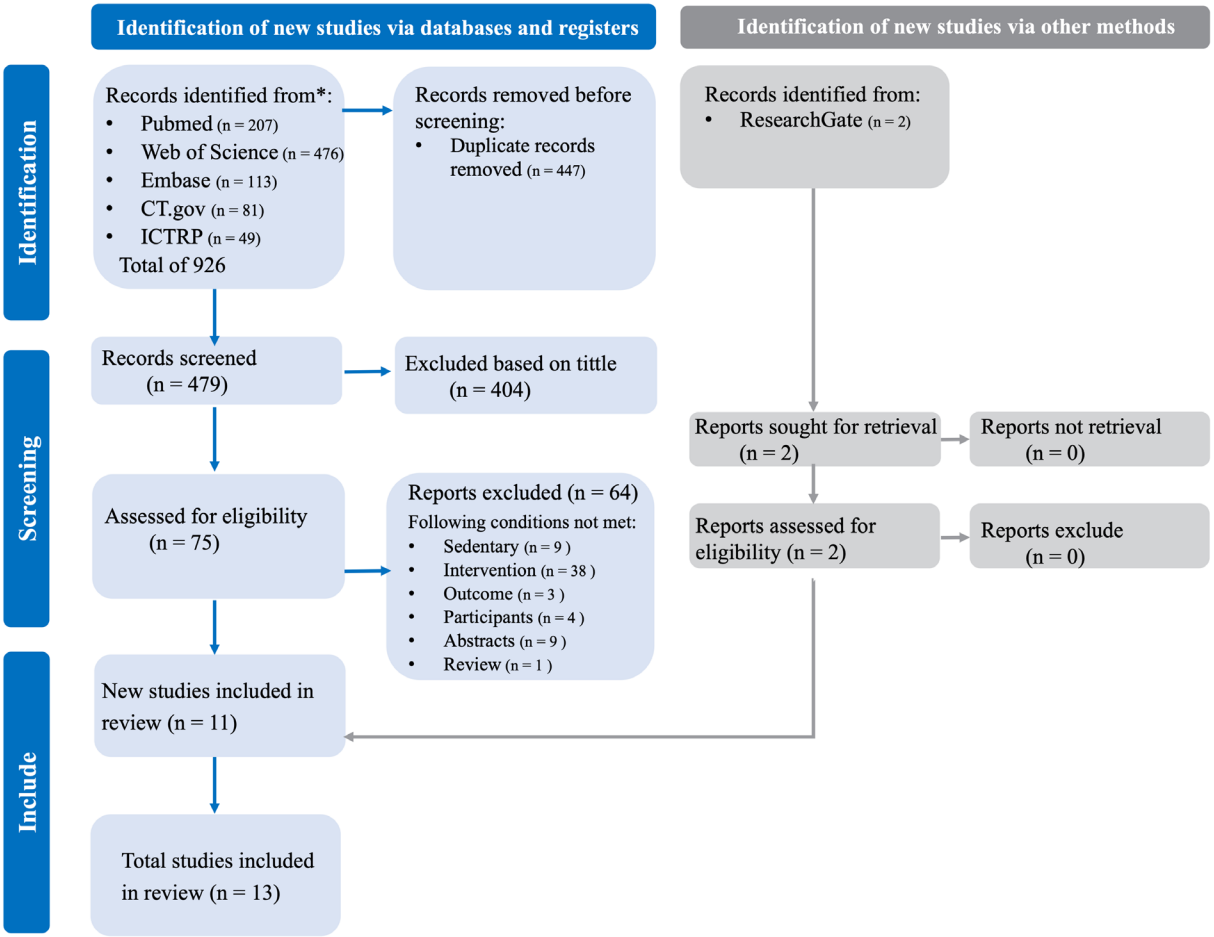

FIGURE 1 | PRISMA flow diagram for included and excluded studies. * Indicates records identified through database searches (PubMed, Web of Science, Embase, CT.gov, ICTRP). These records were aggregated from multiple sources for screening in the systematic review.

and Type 2 diabetic ($n = 4$ studies) [21, 23, 63, 64] participants. The sedentary control time included in the study ranged from 4 to 9 h, and the modes of interruptions were walking (62%), simple resistance activity (23%), and standing (15%), with interruption frequencies every 15 min (15%), 20 min (15%), 30 min (77%), 45 min (15%), 60 min (85%), and 120 min (15%) of sitting, and interruption durations per bout ranging from 1 min to 10 min, respectively. Other participant, intervention, and outcome details are outlined in Table 1.

3.3 | Synthesis of Results

A meta-analysis incorporating nine studies ($k = 25$, 740 participants) that measured glucose as a study outcome showed that interruptions with an HF were significantly superior to LF in terms of reducing glucose levels (Hedge's $g = -0.30$, 95% CI [−0.57, −0.03], $p = 0.03$, power = 87%, Figure 2), with moderate heterogeneity observed (I^2-level 2 = 0%, I^2-level 3 = 42.04%, PI [−1.01, 0.41]). However, there was no difference in insulin, triglyceride, blood pressure, and superficial femoral flow-mediated dilation between the two conditions (Appendix S2).

3.4 | Modifying Factors

Subgroup analyses were conducted to explore modifying effects in the conducted meta-analyses (Table 2). We found a significant modifying effect on mode ($p = 0.01$), where HF interruptions were significantly superior to LF on glucose levels only in studies using walking to interrupt sitting (Hedges' $g = -0.47$), but not in studies using standing (Hedges' $g = -0.28$) nor SRA (Hedges' $g = 0.21$). The differences between the HF and LF conditions for the remaining subgroups were not significant ($p > 0.05$).

For insulin (Table 3), there was a trend for a modifying effect of weight status ($p = 0.06$) wherein interruptions with an HF were significantly greater than LF only in the non-obese (Hedges' $g = -0.84$).

3.5 | Risk of Bias

3.5.1 | Bias and Methodological Issues

The risk of bias for each study is reported in Appendix S3. In the aggregate, the majority of studies (92%) demonstrate "some concerns." 62% of the studies did not report allocation concealment and therefore were considered to be at "some risk" from the randomization process. Almost all studies (92%) did not report the use of rigorous blinding for outcome assessment and were therefore considered "some concern."

Table 4 presents the field-specific issues regarding the methodological design of the study. The most common methodological issue was lack of balance by sex; 62% of the studies did not achieve sex balance. The majority of studies achieved the remaining methodological criteria.

3.5.2 | Risk of Publication Bias

A funnel plot is shown in Appendix S4 and Egger's regression suggested the possible risk of publication bias for glucose (intercept = − 4.72, SE = 0.99, $p < 0.001$) and blood pressure (intercept = −4.78, SE = 1.50, $p < 0.01$) rather than triglyceride (intercept = −1.64, SE = 0.98, $p = 0.12$).

3.6 | Sensitivity Analysis

We conducted a sensitivity analysis comparing the three-level model with a traditional pooled model. The results of the traditional pooled model, provided in Appendix S5, were similar to those of the three-level model in terms of main effect outcomes and statistical significance. Meanwhile, the Hat distance test and studentized residuals did not reveal any outliers. Cook's distance test showed that Homer et al. [64] was an outlier, and after excluding it, there was almost no substantial change in the pooled effect size of glucose (Hedge's $g = -0.37$, 95% CI [−0.62, −0.12], $p < 0.01$).

3.7 | GRADE

The summary of GRADE results (Figure 3) provides an evaluation of the certainty of evidence assessment based on the various outcomes analyzed and subsequent performance. The certainty of evidence was graded as low for all outcomes.

4 | Discussion

In this systematic review and meta-analysis of experimental crossover studies comparing multiple frequencies of sedentary breaks, it was observed that a higher interrupting frequency yielded significantly greater reductions in glucose than a lower frequency, albeit the effect size was relatively small (SMD = −0.30); equivalent to an 11.8% (95% CI: 1.2%–21.6%) reduction in glucose levels [65]. Given that modest improvements in glycemic control are associated with reductions in risk of incident cardiovascular events even in healthy adults, this small advantage may be clinically relevant [66, 67]. However, higher interrupting frequency was not superior to lower interrupting frequency for all other cardiometabolic outcomes. These findings suggest that a higher frequency of sedentary breaks might be more pertinent for glucose management. Given the current absence of meta-analytic evidence supporting specific recommendations on the frequency of sedentary interruptions in guidelines, these findings might provide essential information for practical application and updates to public health guidelines and policies.

4.1 | Glycolipid Metabolism

Previous systematic reviews have confirmed the benefits of interrupting prolonged sitting to improve glucose levels (SMD = −0.54 to −0.36) [10, 11] and have shown that sedentary

TABLE 1 | Participants, interrupting protocol, and outcome characteristics.

Author, year	Participants	Intervention	Outcome	Main finding
Carter et al., 2018 [58]	Healthy workers adults, $n = 15$ (female = 5), age = 36 ± 10, BMI = 25.5 ± 3.2	4-h prolonged sitting; 2-min light-intensity walking breaks every 30 min; sitting with 8-min light-intensity walking breaks every 2 h	Blood flow velocity, BP	Short-duration walking breaks (2 min every 30 min) rather than less frequent longer duration walking breaks (8 min every 120 min) prevented the impairment of MCAv and CA associated with uninterrupted sitting
Carter et al., 2019 [57]	Healthy workers adults, $n = 15$ (female = 5), age = 36 ± 10, BMI = 25.5 ± 3.2	4-h prolonged sitting; 2-min light-intensity walking breaks every 30 min; sitting with 8-min light-intensity walking breaks every 2 h	Femoral artery blood flow, FMD, BP	Longer walking (8 min every 120 min) breaks are more effective than shorter, frequently (2 min every 30 min) ones at mitigating the decline in superficial femoral artery blood flow caused by prolonged sitting
Duran et al., 2023 [59]	Middle- and older age adults $n = 11$ (female = 6), age = 57 ± 9, BMI = 28.3 ± 6.1	8-h prolonged sitting; light-intensity walking every 30 min for 1 min; every 30 min for 5 min; every 60 min for 1 min; every 60 min for 5 min	Glucose (CGM), BP	Only sedentary breaks that were high in frequency (30 min) and duration (1 min or 5 min) yielded significant reductions in glucose relative to an uninterrupted sitting
Homer et al., 2021 [64]	Adult with T2D, $n = 23$ (female = 10), age = 62 ± 8, BMI = 32.7 ± 3.5	7-h prolonged sitting; 3-min SRA (half squats, calf raises, gluteal contractions, and knee raises) every 30 min; and 6-min SRAs every 60 min	Glucose (CGM)	Only less frequent and long-duration interruptions (6 min every 60 min) to sitting may acutely improve glycemic control relative to an uninterrupted sitting
Homer et al., 2021 [21]	Adult with T2D, $n = 23$ (female = 10), age = 62 ± 8, BMI = 32.7 ± 3.5	7-h prolonged sitting; 3-min SRA (half squats, calf raises, gluteal contractions, and knee raises) every 30 min; and 6-min SRA every 60 min	Glucose, insulin, triglyceride	Less-frequent interruptions (6 min every 60 min) rather than high-frequent (3 min every 30 min) to sitting may acutely improve postprandial glycemic response relative to a uninterrupted sitting
Kerr et al., 2017 [31]	Postmenopausal women, $n = 10$ (female = 10), age = 66 ± 9, BMI = 30.6 ± 4.2	5-h prolonged sitting; 2-min standing every 20 min; 10 min standing every hour	Glucose, insulin, triglyceride, FMD, BP	Short, frequent standing breaks (2 min every 20 min) from sitting may improve glycemic response in older female relative to a uninterrupted sitting. Long, less-frequent breaks (10 min every 60 min) may improve vascular health
Ma et al., 2020 [60]	Sedentary healthy adult, $n = 16$ (female = 9), age = 24 ± 3, BMI = 22.2 ± 2.3	9-h prolonged sitting; 3-min of brisk walking (60% VO_2max) in between every 30-min sitting bout; 5-min every 45-min, and 8-min every 60-min	Triglyceride	Only interrupting prolonged sitting with longer walking (8 min every 60 min) reduced the next morning's postprandial serum triglyceride response relative to a uninterrupted sitting

(Continues)

TABLE 1 | (Continued)

Author, year	Participants	Intervention	Outcome	Main finding
Ma et al., 2020 [61]	Sedentary healthy adult, $n = 16$ (female = 9), age = 24 ± 3, BMI = 22.2 ± 2.3	9-h prolonged sitting; 3-min of brisk walking (60% VO_2max) in between every 30-min sitting bout; 5-min every 45-min, and 8-min every 60-min	Glucose, insulin	All three walking-bout conditions improved glycemic metabolism compared with uninterrupted sitting in inactive, healthy adults
Paing et al., 2021 [63]	Adult with T2D, $n = 12$ (female = 4), age = 60 ± 11, BMI = 30.2 ± 4.7	7-h prolonged sitting; 3 min light-intensity walking breaks every 60 min, 30 min, and 15 min	Glucose (CGM)	More frequent interruptions of sedentary time (e.g., every 15 min) with walking breaks may produces better improve glucose control in type 2 diabetes
Taylor et al., 2021 [23]	Adult with T2D, $n = 24$ (female = 11), age = 62 ± 8, BMI = 32.6 ± 3.5	7-h prolonged sitting; 3-min bouts of SRA every 30 min; and sitting with 6-min bouts of SRA every 60 min	Artery blood flow, FMD, BP	Frequent, short-duration SRA breaks (3 min every 30 min) rather than less-frequent breaks (6 min every 60 min) significantly improved vascular function in T2D, suggesting that frequency is more crucial than duration for preventing sitting-induced vascular impairment
Thorsen et al., 2021 [30]	Sedentary, centrally obese men. $n = 14$ (female = 0), age = 28.2 ± 8, BMI = 31.9 ± 6.7	8-h prolonged sitting; 2 min of walking (~30% of VO_2max) every 20 min; 6 min of every hour; 12 min every second hour	Glucose (CGM), insulin	Interrupting prolonged sitting with more frequent activity breaks did not reduce post-meal blood sugar spikes in healthy, sedentary, and centrally obese men
Toledo et al., 2021 [62]	Sedentary and prediabetic adults, $n = 11$ (female = 7), age = 47 ± 11, BMI = 34.6 ± 5.4	7.5-h prolonged sitting; 2.5 min of standing every 15 min; 10 min of standing every hours	Glucose (CGM)	Short, frequent standing (2.5 min every 15 min) to interrupt prolonged sitting improve postprandial glycemic response compared to less-frequent breaks (10 min every 60 min)
Wongpipit et al., 2021 [22]	Men with central obesity, $n = 21$ (female = 0), age = 23 ± 4, BMI = 29.8 ± 3.2	6-h prolonged sitting; 3-min light-intensity walking every 30 min (3 min); and 6-min light-intensity walking every 60 min (6-min)	Glucose, Insulin, Triglyceride	Interrupting prolonged sitting with light-intensity walking, irrespective of the frequency, can reduce postprandial triglyceride. However, its impact on postprandial glucose and insulin appears to be limited

Abbreviations: BP, blood pressure; CA, cerebral autoregulation; CGM, continuous glucose monitor; FMD, flow-mediated dilation; HR, heart rate; MCAv, middle cerebral artery blood flow velocity; SRA, simple resistance activity; T2D, type 2 diabetes.

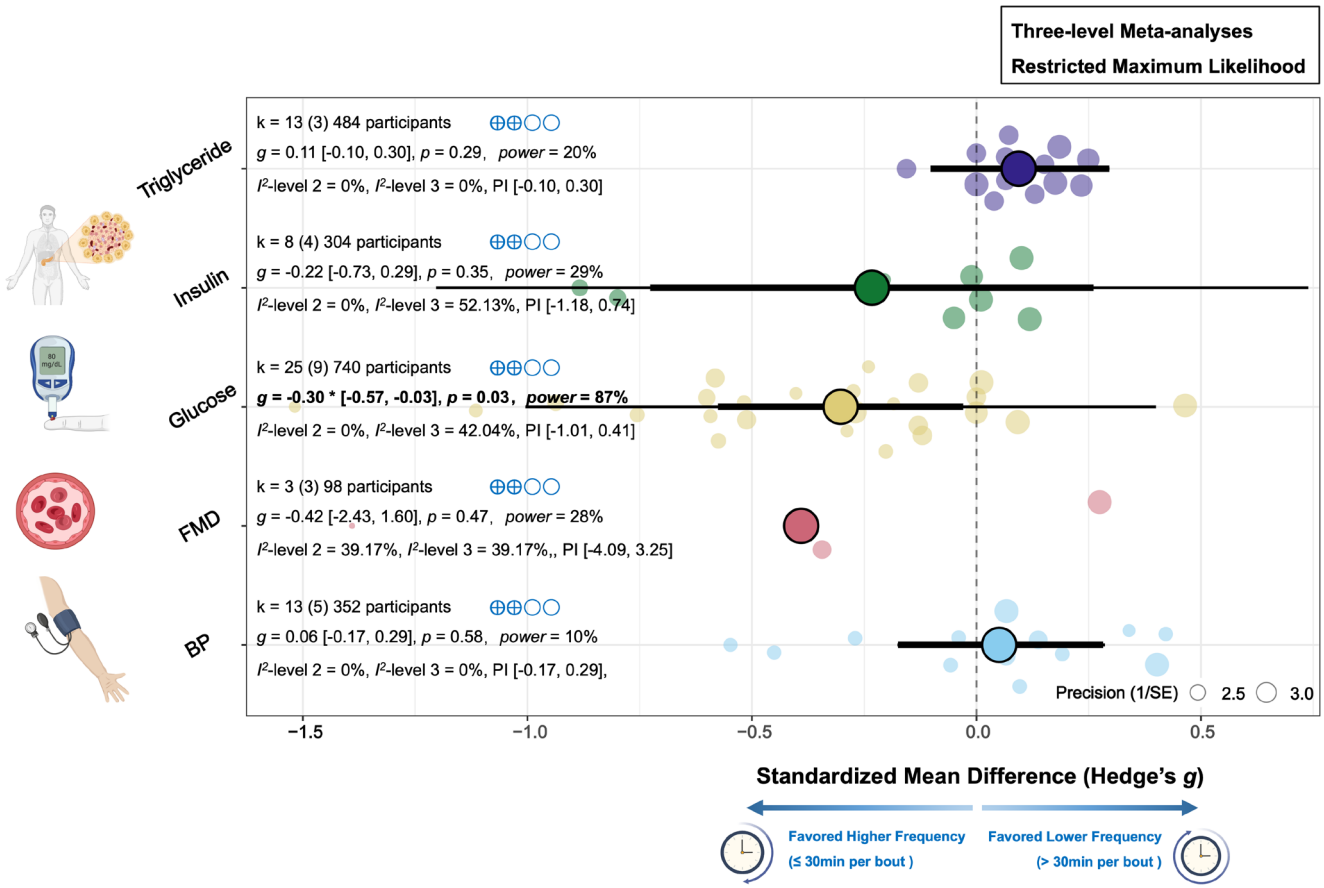

FIGURE 2 | Forest plot of the effects on cardiometabolic health. BP, blood pressure; FMD, femoral flow-mediated dilation.

breaks throughout the day are superior in regulating daily glucose levels than a single session of exercise (SMD = −0.39 to −0.26) [11, 19, 20]. Unfortunately, it was not possible to derive any recommendations regarding the frequency of interruptions from these reviews. The current pooled meta-analytic results indicated that HF (≤ 30 min per bout) had a superior effect on glucose compared to LF (SMD = −0.30). Our results are supported by epidemiological evidence. Prospective cohort studies have demonstrated that accumulating sedentary time in bouts of 60–89 min or ≥ 90 min is associated with an increased risk of all-cause mortality, whereas accumulating sedentary time in bouts < 30 min is linked to a smaller risk [68]. Collectively, these findings suggest that interrupting prolonged sitting more frequently may be a superior strategy compared to less frequent interruptions, particularly for glucose control. Indirectly, they also emphasize that it is advisable to minimize time spent in continuous sedentary activity of 30 min or more.

The current physiological interpretation of differences in glucose-lowering efficacy due to various frequencies remains indirect and speculative. Interrupting every 20 min with a 2-min walk (3.2 km/h) during a 5-h prolonged sitting altered the expression of 10 genes involved in carbohydrate metabolism, including an increase in the expression of the gene dynamin light chain (DYNLL1) that might regulate the translocation of GLUT-4 and pyruvate dehydrogenase kinase 4 (PDK-4), which inhibits the pyruvate dehydrogenase complex and increases glucose utilization [69]. Thus, it has been speculated that more frequent muscle contraction (via more frequent "sit-to-stand" transitions) is required for optimal glucose control. This is supported by evidence demonstrating that frequent interruptions to prolonged sitting, as opposed to a single bout of activity, are more effective in increasing the intensity and duration of local muscle activation patterns [70]. However, no studies have explored the molecular mechanisms underlying the variations in glucose from different frequencies. Further research is warranted.

Effect modification analyses showed that HF/LF differences for glucose were moderated by the mode of sedentary breaks, with HF interruptions being superior to LF interruptions only for walking-based activities (SMD = −0.47), while no differences were observed for standing (SMD = −0.28) and simple resistance activity (SRA, SMD = 0.21). Some caution is warranted with interpreting these findings as the statistical power in the standing and SRA subgroups was low (19%–20%); nonetheless, point estimates show robust HF/LF differences for walking that are smaller in magnitude for standing or favor LF interruptions for SRA. Walking, standing [71], and SRA do not recruit and activate the same types and quantities of muscles, thus the observed effect modification by mode could be partially attributed to differences in muscle activation patterns [70]. Additionally, the acute glycemic response to SRA may partially explain why LF interruptions yield more favorable effects. Previous studies have found that there is a transient increase in glucose immediately after SRA [72]. It should be noted that all comparisons of different frequencies of SRA were derived from a single study by Homer et al. [21, 64], underscoring the need for caution in interpreting

TABLE 2 | Subgroup analyses based on meta-analyses results of glucose.

Subgroup	K (*N*)	Hedges' *g*	95% CI	*t*-value	p_d	I^2-2	I^2-3	Power	p_b
Glucose status									
Normal glucose	15 (440)	−0.37	[−0.74, 0.01]	−2.06	0.05	0%	0%	96%	0.09
Impaired glucose	10 (300)	−0.20	[−0.63, 0.24]	−0.94	0.36	0%	68%	36%	
Sex									
Mixed sex	20 (580)	−0.25	[−0.59, 0.09]	−1.52	0.14	0%	49%	58%	0.23
Male only	4 (140)	−0.43	[−1.07, 0.22]	−1.36	0.18	0%	53%	45%	
Female only	1 (20)	−0.40	[−1.61, 0.80]	n/a	n/a	n/a	n/a	n/a	
Age (years)									
<60	17 (480)	−0.35	[−0.71, 0.02]	−1.98	0.06	0%	0%	28%	0.11
≥60	8 (260)	−0.22	[−0.68, 0.24]	−0.98	0.34	0%	72%	20%	
Weight status									
Non-obese	12 (336)	−0.43	[−0.87, 0.01]	−2.04	0.05	0%	9%	84%	0.09
Obese	13 (404)	−0.21	[−0.57, 0.15]	−1.18	0.24	0%	57%	31%	
Mode									
Walking	18 (516)	−0.47	[−0.77, −0.16]	−3.23	<0.01	0%	32%	99%	0.01
Standing	4 (80)	−0.28	[−0.99, 0.43]	−1.23	0.30	0%	0%	19%	
SRA	3 (144)	0.21	[−0.65, 1.06]	1.03	0.41	0%	21%	20%	
Equivalent duration									
Yes	10 (344)	−0.18	[−0.47, 0.22]	−0.78	0.47	0%	47%	26%	0.07
No	15 (396)	−0.44	[−0.76, −0.10]	−2.75	0.01	0%	29%	95%	

Note: Hedges' *g*: Pooled effect size between the observed effects of HF compared with LF, negative values indicate lower glucose under HF compared with LF; p_d: overall pooled effect; p_b: between subgroups differences.
Abbreviation: SRA, simple resistance activities.

this finding and highlighting the urgent need for future trials to validate these findings. Overall, this subgroup analysis suggests that the frequency and mode of interruption may interact and may need consideration when designing interruption protocols.

4.2 | Vascular Function and Blood Pressure

Previous several systematic reviews have confirmed the benefits of interrupting prolonged sitting on FMD (SMD = 0.84, mean difference = 1.50%–1.74%) [13–15]. However, few studies have attempted to explore the effect of frequency. The current pooled meta-analytic results indicated that HF (≤30 min per bout) had no difference in superficial femoral FMD compared to LF (SMD = −0.42, $p = 0.47$), albeit the heterogeneity was high (I^2-level 2 = 39.17%, I^2-level 3 = 39.17%). Interestingly, we observed effect sizes near the "moderate" range, favoring low-frequency interruptions over high frequency. The lack of observed statistical significance might be due to the low statistical power (28%) of the current pooled result. All three studies included in the pooled analysis were matched for total interruption duration. Therefore, it can be surmised that acute improvement in FMD might require longer single interruption durations rather than higher interruption frequencies. For example, two studies explored the effect of interrupting prolonged sitting through hourly stair climbing on FMD in apparently healthy individuals [73, 74]. Caldwell et al. [74] utilized a short single bout duration (approximately 14–20 s), while Cho et al. [73] used a longer single session duration (5 min). An improvement in FMD (compared to prolonged sitting) was evident only in the study by Cho et al. [73]. Thus, the longer duration per bout might be a crucial factor influencing FMD improvement.

The current pooled meta-analytic results indicated that HF (≤30 min per bout) had no difference in blood pressure compared to LF (Hedge's $g = -0.06$, $p = 0.69$). A previous meta-analysis by Paterson et al. [18] suggested interrupting prolonged sitting with walking significantly lower SBP (mean difference = −4.4 mmHg, SMD = 0.26) and DBP (mean difference = −2.4 mmHg, SMD = 0.19) compared to uninterrupted sitting. In a meta-regression analysis, Adams et al. [17] further revealed that sitting duration is positively associated with increases in peripheral blood pressure Specifically, SBP, DBP, and MAP increased at rates of 0.42, 0.24, and 0.66 mmHg/h, respectively [17]. Thus, in theory, more frequent breaks should be more efficacious in preventing sustained increases in blood pressure. However, our findings do not support this hypothesis.

TABLE 3 | Subgroup analyses based on meta-analyses results of insulin.

Subgroup	K (*N*)	Hedges' *g*	95% CI	*t*-value	p_d	I^2-2	I^2-3	Power	p_b
Glucose status									
Normal glucose	5 (160)	−0.36	[−1.04, 0.32]	−1.31	0.24	0%	51%	39%	0.47
Impaired glucose	3 (144)	0.08	[−0.91, 1.07]	1.89	0.85	0%	0%	6%	
Sex									
Mixed sex	3 (144)	0.08	[−1.31, 1.47]	0.14	0.89	0%	0%	6%	0.77
Male only	4 (140)	−0.42	[−1.46, 0.62]	−1.03	0.35	0%	0%	62%	
Female only	1 (20)	−0.21	[−1.96, 1.55]	n/a	n/a	n/a	n/a	n/a	
Age (years)									
<60 years	4 (140)	−0.41	[−1.17, 0.36]	−1.29	0.24	0%	0%	59%	0.48
≥60 years	4 (164)	−0.02	[−0.82, 0.79]	−0.04	0.96	0%	0%	4%	
Weight status									
Non-obese	2 (56)	−0.84	[−1.52, 0.16]	−3.01	0.02	0%	0%	75%	0.06
Obese	6 (248)	0.02	[−0.29, 0.32]	0.13	0.89	0%	0%	4%	
Mode									
Walking	4 (140)	−0.42	[−1.46, 0.62]	−1.03	0.35	0%	69%	35%	0.77
Standing	1 (20)	−0.21	[−1.96, 1.55]	n/a	n/a	n/a	n/a	n/a	
SRA	3 (144)	0.07	[−1.32, 1.47]	0.14	0.89	0%	0%	5%	

Note: Hedges' *g*: Pooled effect size between the observed effects of HF compared with LF, negative values indicate lower insulin under HF compared with LF; p_d: overall pooled effect; p_b: between subgroups differences.
Abbreviation: SRA, simple resistance activities.

Mechanistically, the seated posture creates bends/constrictions in blood vessels of the lower limbs, eliciting decreased and turbulent blood flow. As a result of insufficient muscle contraction, the seated posture also yields increased hydrostatic pressure and reduced venous return, causing lower limb blood pooling. These hemodynamic conditions occur within 30–60 min of continuous sitting, resulting in increases in peripheral resistance [75]. Although the present study did not evaluate underlying mechanisms, they nonetheless are suggestive that LF sedentary breaks are sufficient to mitigate the BP increases and declines in FMD incurred with prolonged sitting and the concomitant hemodynamic changes.

Due to substantial discrepancies and imprecision in the above outcomes of the aforementioned studies, further research is warranted to investigate the precise effects and potential mechanisms of interruption frequency on vascular function and blood pressure.

4.3 | Current Gaps and Calls for Future Research

Based on the presented meta-analysis, several research gaps have been identified. Firstly, current research on the effects of different frequencies of interruptions on insulin, triglycerides, and blood pressure is still preliminary. The scarcity of available primary studies led to low statistical power in the current meta-analyses, resulting in potentially imprecise meta-analyses pooled results. Further dosing studies on these outcomes are warranted and may have significant practical value for developing quantitative guidelines. Secondly, only three studies to date have tested > 2 doses in a single study and none has tested > 4. Thus, few studies exist that make direct comparisons across multiple doses to inform optimal frequencies. Thirdly, the molecular mechanisms underlying different interruption frequencies remain unknown, necessitating further urgent research. Fourth, there is still limited research on the interaction between the frequency and mode of interruption. For example, the current research comparing different frequencies under SRA is primarily derived from Homer et al. [21, 64] Further trials are needed to clarify this point. Fifth, the acute response to different interruption frequencies on cardiometabolic health was exclusively assessed in a tightly controlled laboratory setting. Whether these findings can be extrapolated to the real world with long-term efficacy remains uncertain. Finally, while findings from this study suggest that higher-frequency sedentary interruptions might yield better results for glucose control, several studies indicate potential issues with the acceptability of such high-frequency interruptions [76]. Thus, there is an urgent need for future randomized controlled trial designs to validate the long-term effectiveness and feasibility, considering quantitative endpoints like adherence, of various frequencies and durations.

4.4 | Strengths and Potential Limitations

This is the first systematic review to evaluate direct (i.e., "head-to-head") comparisons of sedentary interruptions protocols

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

Author, Year	Sex balance	Female hormonal cycle	Objective measurement of SB/PA (prior to)	Abstention MVPA (≥48 h)	Washout period (≥7 d)	Abstention alcohol/ caffeine	Abstention tobacco/ smoking	Diet standardization	Objective measurement of SB/PA (during)
Carter et al., 2018 [58]	−	+	−	−	−	−	+	+	−
Carter et al., 2019 [57]	−	+	−	−	−	−	+	+	−
Duran et al., 2023 [59]	+	−	activPAL	+	+	+	+	+	−
Homer et al., 2021a [64]	+	N/A	activPAL	+	−	+	+	+	activPAL
Homer et al., 2021b [21]	+	N/A	activPAL	+	−	+	+	+	activPAL
Kerr et al., 2017 [31]	−	N/A	−	+	−	−	−	+	−
Ma et al., 2020 [60]	+	+	ActiGraph GT3X	+	+	+	+	+	ActiGraph GT3X
Ma et al., 2020 [61]	+	+	ActiGraph GT3X	+	+	+	+	+	ActiGraph GT3X
Paing et al., 2021 [63]	−	N/A	activPAL	+	+	+	+	+	activPAL
Taylor et al., 2021 [23]	−	+	activPAL	+	+	+	−	+	activPAL
Thorsen et al., 2019 [30]	−	N/A	activPAL3 micro	+	−	+	+	+	activPAL3 micro
Toledo et al., 2023 [62]	−	−	activPAL	+	+	+	−	+	activPAL
Wongpipit et al., 2021 [22]	−	N/A	ActiGraph GT3X	+	+	+	+	+	ActiGraph GT3X

Abbreviations: +, criteria met and/or adequately explained; −, criteria not met or adequately explained; N/A, not applicable.

Outcome	No of participants (studies)	Certainty Assessment					Standardized Mean effect (95% CI) †	GRADE*
		Risk of Bias	Inconsistency	Indirectness	Imprecision	Other		
High-Frequency *versus* Low-Frequency								
Glucose	740 (9 RCTs)	Some serious	Not serious	Not serious	Not serious	Risk of publication bias	-0.30 (-0.57 to -0.03)	⊕⊕◯◯ LOW
Insulin	304 (4 RCTs)	Some serious	Not serious	Not serious	Serious	None	-0.22 (-0.73 to 0.29)	⊕⊕◯◯ LOW
Triglyceride	484 (3 RCTs)	Some serious	Not serious	Not serious	Serious	None	0.11 (-0.10 to 0.30)	⊕⊕◯◯ LOW
Blood Pressure	352 (5 RCTs)	Some serious	Not serious	Not serious	Serious	None	-0.06 (-0.41 to 0.28)	⊕⊕◯◯ LOW
FMD	98 (3 RCTs)	Some serious	Not serious	Not serious	Serious	None	-0.42 (-2.43 to 1.60)	⊕⊕◯◯ LOW

* Certainty of evidence according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE):
High: We are very confident in the estimated effect
Moderate: Our confidence in the estimated effect is moderate
Low: We have limited confidence in the estimated effect
Very low: We have very little confidence in the estimated effect
No of participants: Total number of participants with pooled effects

FIGURE 3 | Certainty of evidence. †The standardized mean effect was calculated as the difference in the degree of change in high-frequency low-duration versus low-frequency high-duration. FMD, superficial femoral flow-mediated dilation; RCTs, randomized crossover trial.

of varying frequency on cardiometabolic health; information vital to informing appropriate sedentary break dosing for future guidelines/recommendations. The studies incorporated into this review all consisted of randomized crossover trials and largely featured methodologically rigorous study design elements. Effect modification and subgroup analyses were also conducted to elucidate potential sources of heterogeneity in dose effectiveness, offering information necessary to develop more precise practical applications.

Nevertheless, several limitations should be noted. First, only 13 peer-reviewed published studies were identified. The small number of studies limited statistical power and precision in our pooled effect sizes and subgroup analyses. Second, we excluded non-English studies and gray literature, but this potential risk of bias is unlikely to influence our pooled effect size. Thirdly, we observed some evidence for publication bias. However, given the small sample size, the Egger test may produce a false-positive indication of bias and should be interpreted with caution [77]. Fourth, there was heterogeneity concerning participant characteristics and interruption protocols. While we addressed some of this potential heterogeneity through subgroup and sensitivity analyses, some caution is still warranted in interpreting the study results. Lastly, several interruption protocols did not align in the total duration of sedentary breaks between conditions [31, 59, 61, 63]. This creates uncertainty regarding whether the beneficial effects of a given dose are driven by differences in total physical activity duration, sitting time, or energy expenditure. However, we conducted a sensitivity analysis excluding studies with highly heterogeneous participants (T2D) and different total interruption durations. Despite this, the higher interruption frequency was more efficacious than the lower frequency for glucose reduction (Hedge's $g = -0.43$, 95% CI [−0.83, −0.04], $p = 0.03$, $I^2 = 0\%$), verifying our conclusions.

5 | Conclusion

In this systematic review and meta-analysis of 13 experimental crossover studies comparing multiple frequency/duration doses of sedentary breaks, it was observed that a higher interrupting frequency was more efficacious than a lower frequency for the reduction in glucose. No differences between strategies (HF vs. LF) were observed for insulin, triglycerides, blood pressure, and vascular function. These findings suggest interruptions at a high frequency (every 30 min) or minimizing time spent in continuous sedentary activity < 30 min be an ideal protocol for glucose control.

6 | Perspective

Sedentary behavior affects insulin sensitivity and elevates blood glucose levels [78], which is associated with an increased risk of various chronic diseases and mortality [79]. Managing cardiometabolic health by interrupting or reducing prolonged sitting is a simple and feasible strategy that may offset some of these harms. Our findings indicate that higher frequency interruptions provide better acute glycemic improvements when using an interrupting prolonged sitting strategy. In the high-frequency studies we included, their duration per bout ranged from 1 to 5 min, with a mean of 2.7 min. Although it is not possible to fully determine whether this is the minimum or optimal threshold of effectiveness at this frequency (≤ 30 min per bout, HF), the acute advantage of these protocols on glucose is supported. Recent randomized controlled trials have confirmed that short-bout, multiple-times-a-day exercise (exercise snacks [80, 81]) can produce long-term benefits for cardiometabolic health (e.g., VO_2peak) [81], comparable to the aerobic exercise recommended in traditional guidelines [82]. Additionally, evidence from prospective cohort studies

suggested that accumulating moderate- to high-intensity activity for as little as 1 min a few times a day significantly reduces cardiovascular incidence [83], cancer incidence [66], and cardiovascular, cancer, and all-cause mortality [84]. These findings extend the value and scope of the application of the results of this study.

Acknowledgments

The authors wish to express their highest respect to the editors and reviewers for their insightful suggestions. The authors would appreciate the beautiful vectors provided on biorender.com.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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