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Title: The effects of acute exposure to prolonged sitting, with and without interruption, on peripheral blood pressure among adults: A systematic review and meta-analysis

Running head: Acute sitting exposure and blood pressure

Type: Systematic Review

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Abstract

Background: Previous reviews have shown that exposure to acute prolonged sitting can have detrimental effects on several cardiovascular and cardiometabolic health markers. However, to date there has been no synthesis of peripheral blood pressure data (including systolic [SBP], diastolic [DBP], and mean arterial pressure [MAP]), an important and translatable marker of cardiovascular health. Similarly, no previous study has consolidated the effects of sitting interruptions on peripheral blood pressure.

Objectives: (1) To assess the effect of exposure to acute prolonged sitting on peripheral blood pressure, and (2) to determine the efficacy of sitting interruption strategies as a means of offsetting any negative effects. Subgroup analyses by age and interruption modality were performed to explore heterogeneity.

Data Sources: Electronic databases (PubMed, Web of Science, and SportDiscus) were searched from inception to March 2021. Reference lists of eligible studies and relevant reviews were also screened.

Study Selection: Inclusion criteria for objective (1) were: (i) peripheral blood pressure was assessed non-invasively in the upper limb pre- and post-sitting; (ii) studies were either randomised controlled, randomised crossover, or quasi-experimental pre- versus post-test trials; (iii) the sitting period was ≥1 hour; (iv) pre- and post-sitting measures were performed in the same posture; (v) participants were adults (≥18 years), free of autonomic or neuromuscular dysfunction. Additional criteria for objective (2) were: (i) the interruption strategy was during the sitting period; (ii) there was an uninterrupted sitting control condition; (iii) the interruption strategy must have involved participants actively moving their upper or lower limbs.

Appraisal and synthesis methods: 9763 articles were identified, of which 32 met inclusion criteria for objective (1). Of those articles, 22 met inclusion criteria for objective (2). Weighted mean difference (WMD), 95% confidence intervals (95% CI), and standardised mean difference (SMD) were calculated for all trials using inverse variance heterogeneity meta-analysis modelling. SMD was used to determine the magnitude of effect, where <0.2, 0.2, 0.5, and 0.8 were defined as trivial, small, moderate, and large, respectively.

Results: (1) Prolonged uninterrupted sitting resulted in trivial and small significant increases in SBP (WMD=3.2 mmHg, 95% CI:0.6 to 5.8, SMD=0.14) and MAP (WMD=3.3 mmHg, 95% CI:2.2 to 4.4, SMD=0.37), respectively, and a non-significant trivial increase in DBP. Subgroup analyses indicated that the increases in SBP and MAP were more pronounced in younger age groups. (2) Interrupting bouts of prolonged sitting resulted in significantly lower SBP (WMD=-4.4 ~~3~~mmHg, 95% CI:-7.4 to -1.5, SMD=0.26) and DBP (WMD=-2.4 mmHg,

95% CI:-4.5 to -0.3, SMD=0.19) compared to control conditions, particularly when using aerobic interruption strategies.

Conclusions: Exposure to acute prolonged uninterrupted sitting results in significant increases in SBP and MAP, particularly in younger age groups. Regularly interrupting bouts of prolonged sitting, particularly with aerobic interruption strategies may reduce negative effects.

Conflicts of interest: None

Source of funding: None

Key Points

There is mounting evidence that bouts of prolonged uninterrupted sitting can have detrimental effects on a number of cardiovascular and cardiometabolic outcomes. However, to date, there has been no consolidation of the existing data related to peripheral blood pressure, an important and easily translatable measure of cardiovascular health.

This meta-analysis shows that bouts of prolonged uninterrupted sitting may result in increased SBP and MAP, particularly in younger age groups and that regularly interrupting those sitting bouts with aerobic interruption strategies may prevent it.

Future work should aim to identify optimum frequencies, intensities, and timings of sitting interruption strategies.

1. INTRODUCTION

Increased time spent in sedentary behaviours, defined by posture (seated, reclined, or lying) and low energy expenditure (≤1.5 metabolic equivalents)[1], is associated with increased cardiovascular disease risk and all-cause mortality[2,3]. Previous reviews have identified several indices of cardiometabolic health that are negatively affected by acute bouts of prolonged (≥1 hr) uninterrupted sitting, including vascular [4] and metabolic responses[5–8]. Additionally, multiple studies have demonstrated an increase in peripheral blood pressure over the course of a single bout of prolonged uninterrupted sitting [9–22]. However, no previous meta-analysis has consolidated the literature to quantify the expected blood pressure response to prolonged sitting.

Sedentary behaviours, particularly prolonged sitting, comprise a large portion of the day for people across many societies [23–31]. As such, it is critical that the physiological consequences of this ubiquitous behaviour on the cardiovascular system are better understood. This understanding is required to not only guide intervention development, but also to establish biological plausibility and inform policy [32]. Blood pressure reflects the amount of force exerted on vessel walls by the blood, whilst also indicating the acute burden on vital end-organs such as the brain and kidneys [33–35]. As a function of sedentary behaviour, it is conceivable that many individuals are repeatedly exposed to prolonged elevations in blood pressure both daily and cumulatively. This is of particular concern as epidemiological data suggests that long term increases in blood pressure are associated with increased incidence of CVD [36], though it should be noted that the prognostic value of sitting-induced elevation in blood pressure are as yet unknown. It is also plausible that the blood pressure response to prolonged sitting is moderated by demographic factors, including aging. Different age groups may experience varying effects of prolonged uninterrupted sitting as a function of the age-related changes to the vascular system and blood pressure regulation [37,38].

Previous reviews have demonstrated that regularly interrupting bouts of prolonged sitting with aerobic interruption strategies, such as walking, can offset some of the deleterious effects on cardiometabolic health [4–8]. It is therefore plausible that similar strategies may help to offset any detrimental effects on peripheral blood pressure. As national and international guidelines begin to implement recommendations for interrupting prolonged sitting periods [39–41], understanding which strategies may be most effective in preventing sitting-induced blood pressure elevations is an important step in informing future policy and guidelines. Therefore, it is also necessary to consolidate the existing literature investigating how regularly interrupting bouts of prolonged sitting may affect peripheral blood pressure.

1.2 Objectives

The objectives of this meta-analysis were two-fold: (1) determine the effect of uninterrupted sitting on peripheral blood pressure, with subgroup analysis to identify whether age of participants helped to explain heterogeneity; and (2) to conduct a separate meta-analysis to determine the effect of sitting interruption strategies on peripheral blood pressure, with subgroup analysis of sample age and interruption strategy type.

2. METHODS

This systematic review and meta-analysis was reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [42], however it was not pre-registered.

2.1 Data Sources and Searches

Electronic databases (PubMed, Web of Science, and SportDiscus) were searched by two authors (CP and LS). As peripheral blood pressure is frequently assessed as a secondary, as well as primary outcome measure the search terms utilised reflected the need to capture all relevant literature related to prolonged sitting, cardiovascular and cardiometabolic health. The reference lists of all relevant articles and reviews were also examined. The search was limited to English language studies published between inception and March 2021. Full details of the search strategy are presented in Electronic Supplementary Material Appendix S1.

2.2 Article Selection

For this meta-analysis, the terms ‘study’ and ‘article’ are used interchangeably, whereas ‘trial’ refers to the unit included in the meta-analysis. As such, a given study can comprise multiple eligible trials, for example separate independent samples within a study (for example, males vs females). After the primary searches were complete, duplicate studies were removed and study titles and abstracts were screened for relevance. After this initial screening, the full texts of potentially eligible articles were reviewed for inclusion. The following criteria were used to select trials for inclusion: (i) peripheral blood pressure (systolic [SBP], diastolic[DBP], or mean arterial pressure [MAP]) was measured non-invasively in the upper limb pre- and post-sitting; (ii) studies were either randomised controlled, randomised crossover, or quasi-experimental pre- versus post-test trials; (iii) the prolonged sitting period was at least one hour; (iv) pre- and post-sitting blood pressure assessments were performed in the same posture; (v) participants were adults ($\geq$ 18 years), free of autonomic or neuromuscular dysfunction and any other known chronic illness. It should be noted that trials were still included in the analysis for objective (1) if

restroom and water breaks were permitted during the sitting period as these were deemed to not represent sitting interruption strategies.

To address the second objective of this review, further additional inclusion criteria were used; (i) if a strategy was employed to disrupt the effects of sitting, the strategy must have been during the sitting period; (ii) there must have been a control (uninterrupted sitting) group or condition, and (iii) the interruption strategy must have involved the participants actively moving their limbs. If a study employed an intervention prior to or after the sitting period, only data from the control (uninterrupted sitting) trial was included in the analysis. Study selection was completed independently by two researchers (CP and LS).

2.3 Data Extraction and Quality Assessment

Data extracted for each eligible trial included bibliographic information (author, publication year), collected measures, sample characteristics (age, sex, body mass index [BMI], etc.), details of any interventions, and pre- and post-sitting peripheral blood pressure values. If data were presented as figures, values were extracted using ImageJ image analysis software [43]. This method of extracting data inevitably introduces a degree of error. To quantify the likely amount of measurement error introduced, those researchers extracting data completed tests of reliability and validity on existing known data sets from previous projects conducted by our group. Researchers extracted data three times from four published figures, closing and recalibrating extraction software each time. Researchers completed these extractions independently and were blinded to the true data values and each other's extracted values throughout. Comparison of extracted values to known data values showed excellent validity and reliability for both researchers (CP, ICC = 0.99, r = 0.99, and GZ, ICC = 0.99, r = 0.99) [44]. Inter-rater reliability was then assessed using a two-way mixed, absolute agreement, average-measures ICC to assess the degree of consistency between researchers. The ICC (0.99) indicated that minimal measurement error was likely to have been introduced [44]. Data extraction was completed independently by two researchers (CP and GZ) and checked for agreement.

Study quality was assessed using a modified Heyland Methodological Quality Score (HMQS) [45,46] with a maximum score of 9. The HMQS criteria "blinding", "extent of follow up", and "outcomes" were not considered for the current analysis as these criteria are for longitudinal study designs. Quality assessment was conducted independently by two researchers (CP and KS), with a third researcher (SF) acting as an adjudicator in the event of a lack of consensus.

2.4 Data Synthesis

For the primary outcomes, the pre- and post-intervention values (mean and standard deviation) as well as mean difference and associated standard deviations were entered into a spreadsheet. When data were not published, a request for missing data was made to the corresponding author and following a non-response, the values were estimated based on methods described within the Cochrane Handbook for Systemic Reviews of Interventions.[47] For trials reporting multiple time points, only pre- and post-sitting values were used in analysis. Aggregation and calculation of final results was conducted by two authors (CP and LS).

2.5 Data Analysis

Data was analysed using the 'metafor' package (version 2.4.0) [48] in R (version 4.0.3) [49]. Outcome measures were expressed as weighted mean difference (WMD) and standardised mean difference (SMD), expressed as Cohen's *d* [50]. The SMD was used to assess the magnitude of effect, where < 0.2, 0.2, 0.5, and 0.8 was defined as trivial, small, moderate, and large respectively [50]. Data were pooled using the inverse variance heterogeneity (IVhet) model of meta-analysis to account for potential heterogeneity within and between studies. This method has been shown to be an suitable alternative to the more traditional random-effects model, which has been suggested to produce overconfident estimates when using heterogenous data [51]. Corresponding forest plots for each analysis were also generated.

Subsequent to running the IVhet models, we examined the robustness of the pooled results, the potential for publication bias, and explored potential sources of heterogeneity. Potential outliers or influential trials were examined using studentised residuals and Cook's distances [52]. If a trial was identified as influential or a potential outlier, the model was repeated with the trial omitted in order to test the robustness of the overall effect. Small-study bias was adjudicated using the Luis Furuya Kanamori (LFK) indexes in tandem with Doi plots [53]. Doi plots are reported to be more objective than traditional funnel plots, which are assessed qualitatively, and the LFK index has been shown to be a more sensitive measure of small-study bias than the traditional Egger's regression [53]. Using this method, $<\pm1$ indicates no asymmetry, ±1 to ±2 suggests minor asymmetry, and $>\pm2$ indicates major asymmetry [53]. Last, statistical heterogeneity was assessed using the I^2 statistic, where <25%, 50%, and 75% represent low, moderate, and considerable heterogeneity, respectively [54]. Heterogeneity $\geq$25% was assumed to indicate that effect sizes could not be treated as estimates of one common effect size, justifying *a priori* determined sub-group analysis. Data analysis was conducted by two authors (CP and LS).

3. RESULTS

3.1 Literature Search and Trial Selection

The literature search strategy and outcomes are outlined in Fig 1. Initial database searches identified a total of 9,763 potentially eligible articles with no additional ones identified through manual searches. Following removal of duplicates and initial screening of titles and abstracts, 9,680 articles were excluded as they failed to meet all inclusion criteria. The remaining 83 articles were subjected to full text screening and 50 further studies were excluded,-bringing the total to 33 individual articles. The final analyses for objective (1) included 24 trials (21 articles) for SBP, 22 trials (20 articles) for DBP, and 26 trials (20 articles) for MAP. The final analyses for objective (2) included 31 trials (17 articles) for SBP and 27 trials (16 articles) for DBP. Fourteen trials (9 articles) reported MAP data, however, owing to the limited number of articles, meta-analysis was not performed.

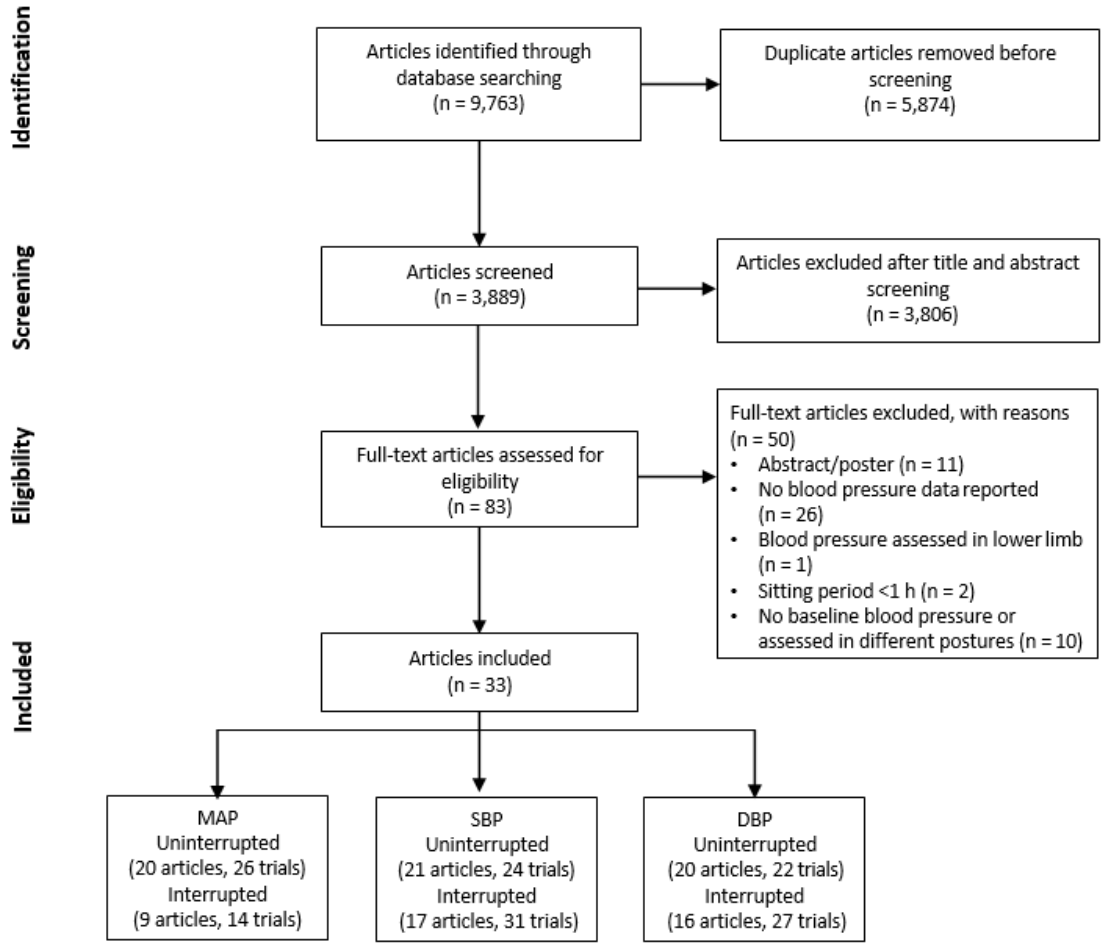

Fig. 1 Flow chart of study selection

Abbreviations: MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

3.2 Characteristics of Included Studies

Trial characteristics are summarised in Table 1.

Systolic Blood Pressure

A total of 24 trials (21 articles) were included in this analysis. The number of participants in each trial ranged from 6 [55] to 67 [56]. Of the 24 trials, 19 included both male and female participants [9,55,20,57–59,11,60,61,21,62,13,63–65,56,66,22], 4 included only females [17,18,67], and one included only males [18]. Bouts of prolonged sitting ranged from 2.5 [61] to 10 hours [60], with a modal duration of three hours. Average ages ranged from 21.7 [11] to 71 [66] years and BMI ranged from 23 [59] to 33 [58] $kg.m^2$.

Of the 21 articles that reported SBP outcomes, 17 (31 trials) included sitting interruption strategies [9,11,13,20–22,55,57–60,62–67]. These interruption strategies included walking or running [13,20,22,55,58,60,63,65–67], cycling [22,59,62], standing breaks [9,22,62,66,67], seated calf-raises [11], and simple resistance activities [21,57,58,64]. For subgroup analysis, all sitting interruption strategies including walking or running, and cycling were grouped together as an 'aerobic interruption strategy' subgroup. Further, simple resistance activities and seated calf raises were group together as a "simple resistance activities" subgroup.

Diastolic Blood Pressure

A total of 22 trials (20 articles) were included in this analysis. The number of participants in each trial ranged from 6 [55] to 67 [56]. Of the 22 trials, 17 included both male and female participants [9,11,13,20–22,55–65], 4 included only females [17,18,67], and one included only males [18]. Bouts of prolonged uninterrupted sitting ranged from 2.5 [61] to 10 hours [60], with a modal duration of 3 hours. Average age ranged from 21.7 [11] to 67 [56] years and BMI from 23 [59] to 33 [58] $kg.m^2$.

Of the 20 articles that reported DBP, 16 (27 trials) assessed sitting interruption strategies. These interruption strategies included various intensities and durations of walking or running [13,20,22,55,58,60,63,65,67], cycling [22,59,62], simple resistance activities [21,57,58,64], seated calf-raises [11], and standing breaks [9,22,62,67]. For subgroup analysis, all sitting interruption strategies including walking or running, and cycling were grouped together as an 'aerobic interruption strategy' subgroup. Further, simple resistance activities and seated calf raises were group together as a "simple resistance activities" subgroup.

Mean Arterial Pressure

A total of 26 trials (20 articles) were included in this analysis. The number of participants in each trial ranged from 6 [55] to 25 [9]. Of the 25 trials, 16 included both male and female participants [9–15,55,60,61,68–71], 5

Table 1 Characteristics of the included trials

Ref	Quality	Sample [n (F); mean age, years (SD)]	Body Mass Index [kg.m^2] Mean (SD)	Reported BP outcomes	Sitting duration (h)	Interruption strategy
Ballard et al. [72]	6	11 (0); 21.2 (1.9)	24.7 (1.0)	MAP	3	N/A
Barone Gibbs et al. [9]	8	25 (9); 42 (12)	31.9 (5.0)	SBP, DBP, MAP	7	Standing
Bhammar et al. [54]	5	6 (2); 32 (5)	30.3 (4.6)	SBP, DBP, MAP	9	Aerobic
Carter et al. [10]	7	15 (5); 35.8 (10.2)	25.5 (3.2)	MAP	4	Aerobic
Carter et al. [67]	7	10 (4); 27.3 (8.1)	NR	MAP	1.5	SRA
Champion et al. [20]	8	24 (12); 35.8 (14.7)	25.7 (4.8)	SBP, DBP	6.5	Aerobic
Charlett et al. [69]	8	12 (7); 25 (6)	24.7 (4.9)	MAP	5	SRA
Climie et al. [56]	9	19 (8); 57 (12)	30.3 (3.4)	SBP, DBP	5	SRA
Credeur et al. [68]	5	20 (7); 26 (7)	30.0 (7.0)	MAP	3	N/A
Decker et al. [71]a	6	12 (0); 25 (4)	22.0 (2.0)	MAP	1.5	N/A
Decker et al. [71]b	6	14 (14); 23 (3)	26.0 (3.0)	MAP	1.5	N/A
Dempsey et al. [57]	9	24 (10); 62 (6)	33.0 (3.4)	SBP, DBP	8	Aerobic and SRA
Dogra et al. [58]	5	10 (5); 24.7 (3)	23.0 (2.1)	SBP, DBP	4	Aerobic
Evans et al. [11]	8	20 (14); 21.7 (2.5)	25.5 (6.1)	SBP, DBP, MAP	3	Aerobic
Freire et al. [59]	7	25 (15); 24.4 (3.8)	26.1 (3.4)	SBP, DBP, MAP	10	Aerobic
Garten et al. [12]a	5	10 (2); 25 (3.2)	23.0 (6.3)	MAP	3	N/A
Garten et al. [12]b	5	10 (2); 25 (3.2)	25.0 (3.2)	MAP	3	N/A
Hartman et al. [70]	7	24 (15); 65 (5)	29.8 (3.9)	MAP	3	Aerobic
Headid et al. [60]	3	12 (6); 22.3 (2)	23.9 (3.0)	SBP, DBP, MAP	2.5	N/A
Kerr et al. [66]	8	10 (10); 66 (9)	30.6 (4.2)	SBP, DBP	5	Aerobic and Standing

Kowalsky et al. [21]	8	14 (12); 53.4 (9.5)	30.9 (4.8)	SBP, DBP	4	SRA
Kruse et al. [61]	8	13 (3); 38 (3)	29.7 (2.0)	SBP, DBP	4	Aerobic and Standing
Larsen et al. [13]	9	19 (8); 53.8 (4.8)	31.2 (3.9)	SBP, DBP, MAP	5	Aerobic
Morishima et al. [14]	6	15 (5); 26.7 (0.5)	25.6 (0.5)	MAP	3	N/A
Morishima et al. [15]a	6	10 (0); 19.7 (0.6)	22.5 (2.3)	MAP	3	N/A
Morishima et al. [15]b	6	9 (0); 21.1 (1.8)	24.8 (1.5)	MAP	3	N/A
Morishima et al. [16]	7	9 (0); 21.2 (2)	22.0 (3.0)	MAP	3	N/A
O'Brien et al. [17]a	7	9 (9); 23 (3)	24.5 (3.0)	SBP, DBP, MAP	3	N/A
O'Brien et al. [17]b	7	9 (9); 23 (3)	23.6 (2.8)	SBP, DBP, MAP	3	N/A
O'Brien et al. [18]a	6	10 (10); 23 (2)	24.2 (3.2)	SBP, DBP, MAP	3	N/A
O'Brien et al. [18]b	6	10 (0); 24 (2)	26.6 (2.0)	SBP, DBP, MAP	3	N/A
Peddie et al. [62]	9	18 (7); 23.5 (5)	23.7 (2.6)	SBP, DBP	6	Aerobic
Taylor et al. [63]	9	24 (11); 61.5 (7.8)	32.6 (3.5)	SBP, DBP	7	SRA
Vranish et al. [19]a	6	12 (12); 20 (0)	24.0 (2.8)	MAP	3	N/A
Vranish et al. [19]b	6	8 (0); 22 (1)	25.7 (2.6)	MAP	3	N/A
Wennberg et al. [64]	9	19 (9); 59.7 (8.1)	31.5 (4.7)	SBP, DBP	7	Aerobic
Wheeler et al. [55]	9	67 (35); 67 (7)	31.2 (4.1)	SBP, DBP	8	Aerobic
Yates et al. [65]a	9	30 (15); 69 (6.7)	26.7 (4.3)	SBP	7.5	Aerobic and Standing
Yates et al. [65]b	9	30 (14) ; 71 (6.7)	26.5 (2.4)	SBP	7.5	Aerobic and Standing
Zeigler et al. [22]	6	9 (7) ; 30 (15)	28.7 (2.7)	SBP, DBP	8	Aerobic and Standing

Abbreviations: F, females; SD, standard deviation; BP, blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SRA, simple resistance activities; NR, not reported; N/A, not applicable, i.e. no interruption strategy. Quality was assessed using a modified Heyland Methodological Quality Score, with a maximum score of 9. Labels a and b denotes different trials from the same study.

included only females [17–19,72], and 5 included only males [16,18,19,72,73]. Bouts of prolonged uninterrupted sitting ranged from 1.5 [68,72] to 10 [60] hours, with a modal duration of 3 hours. Average age ranged from 19.7 [15] to 65 [71] years and BMI ranged from 22 [16,72] to 31.9 [9] $kg.m^2$.

Of the 20 articles that reported MAP, 9 (14 trials) assessed sitting interruption strategies. Sitting interruption strategies included seated calf-raises [11], standing breaks [9], simple resistance activities [68,70], and walking [10,13,55,60,71].

3.3 Methodological Quality Assessment

The methodological quality assessment of included trials is summarised in Table 1. The quality in studies ranged from 3 to 9, with a maximum score of 9 available. The average methodological quality score across all trials was 7, with a modal score of 8, indicating that most trials were of moderate to high methodological quality.

3.4 Synthesis of the Results

3.4.1 Sitting without interruption

Prolonged uninterrupted sitting resulted in a trivial significant increase in SBP (WMD = 3.2 mmHg, 95% Confidence Intervals [95% CI]: 0.6 to 5.8, $p = 0.016$, SMD = 0.14) (Electronic Supplementary Material Appendix S2). Three trials were identified as potentially influential [17,18,56], though omission of each of these trials did not significantly affect the observed result. Visual inspection of Doi plot and an LFK index of -0.21 indicated no asymmetry. The heterogeneity was moderate ($I^2 = 60\%$, $p < 0.001$), justifying subgroup analysis. Subgroup analysis by age is presented in Table 2.

Prolonged uninterrupted sitting resulted in a trivial non-significant increase in DBP (WMD = 0.1 mmHg, 95% CI: -1.3 to 1.6, $p = 0.864$, SMD = 0.00) (Electronic Supplementary Material Appendix S3). No trials were identified as a potential outlier or influential, and visual inspection of Doi plot and an LFK index of -0.44 indicated no asymmetry. The heterogeneity in this analysis was low ($I^2 = 24\%$, $p = 0.150$).

Prolonged uninterrupted sitting resulted in a small and significant increase in MAP (WMD = 3.3 mmHg, 95% CI: 2.2 to 4.4, $p < 0.001$, SMD = 0.37) (Electronic Supplementary Material Appendix S4). Two trials were identified as potentially influential [17,61], though omission of each of these trials did not significantly affect the observed result. Visual inspection of Doi plot and an LFK index of -0.75 indicated no asymmetry. The heterogeneity in this analysis was low ($I^2 = 0\%$, $p = 0.669$). Subgroup analysis by age is presented in Table 2.

Table 2 Meta-analyses of the effect of uninterrupted sitting on systolic blood pressure and mean arterial pressure with subgroup analysis by age

	Pooled Effect					Heterogeneity			Asymmetry			
	WMD	LCI	UCI	P Value	SMD	Q	P Value	I^2	LFK	Quality	Trials	Sample
SBP	3.17	0.58	5.76	0.016	0.14	57.8	<0.001	60	-0.21	8	24	450
Age (years)												
18-24	5.94	1.98	9.90		0.38	22.3	<0.001	64		7	9	117
25-44	4.72	0.50	8.95		0.36	1.86	0.76	0		8	5	77
45-64	4.45	0.11	8.79		0.30	6.09	0.19	34		9	6	95
65+	-2.63	-5.32	0.06		-0.23	2.21	0.70	0		9	4	161
MAP	3.27	2.17	4.37	<0.001	0.37	21.4	0.669	0	-0.75	6	26	331
Age (years)												
18-24	3.71	2.31	5.10		0.50	15.1	0.37	7.5		6	15	173
25-44	2.30	0.15	4.46		0.23	4.88	0.77	0		6	9	125
45-64	1.24	-7.36	9.84		0.09	N/A	N/A	N/A		9	1	19
65+	3.00	-2.54	8.54		0.40	N/A	N/A	N/A		7	1	14

Abbreviations: SBP, systolic blood pressure; MAP, mean arterial pressure; WMD, weighted mean difference; LCI, lower confidence interval; UCI, upper confidence interval; SMD, standardised mean difference; LFK, Luis Furuya-Kanamori Index. SMD: Trivial, small, moderate and large effect sizes are defined as <0.2, 0.2, 0.5, and 0.8 respectively. LFK: <±1 indicates no asymmetry, ±1 to ±2 suggests minor asymmetry, and >±2 indicates major asymmetry. I2: 25%, 50%, and 75% represent low, moderate, and high heterogeneity respectively. Quality is median quality score of included trials assessed using Heyland Methodological Quality Score, with a maximum score of 9.

3.4.2 Sitting with interruption

Across sitting interruption strategies, SBP was significantly lower for the interruption compared to non-interruption condition (WMD = -4.4 mmHg, 95% CI: -7.4 to -1.5, p = 0.003, SMD = 0.26) (Electronic Supplementary Material Appendix S5). Two trials from the same study were identified as potential outliers and potentially influential [58]. The Doi plot and an LFK index of -0.44 indicated no asymmetry. The heterogeneity in this analysis was moderate (I^2 = 70%, p <0.001). Subgroup analysis by interruption strategy is presented in Table 3. Omission of each of the potentially influential/outlier trials individually did not affect statistical significance of the model but did have a substantial effect on the observed outcome and heterogeneity (WMD = -3.1 mmHg 95% CI: -5.4 to -0.8, p = 0.009, I^2 = 52%, and WMD = -3.2 mmHg, 95% CI -5.6 to -0.8, p = 0.010, I^2 = 54%). In the interests of rigour, the analysis was repeated with the omission of both trials and the pooled effect was reduced to a trivial significant difference between interrupted and uninterrupted sitting conditions (WMD = -1.6 mmHg, 95% CI: -3.2 to -0.01, p = 0.049, SMD = -0.14, I^2 = 0%). Subgroup analysis by interruption strategy was repeated with the omission of the influential trials (Table 3).

Across sitting interruption strategies, DBP was significantly lower for the interruption compared to non-interruption condition (WMD = -2.4 mmHg, 95% CI: -4.5 to -0.3, p = 0.022, SMD = -0.19) (Electronic Supplementary Material Appendix S6). Two trials from the same study were identified as potential outliers and potentially influential [58]. Doi plot and an LFK index of 0.93 indicated no asymmetry. The heterogeneity in this analysis was moderate (I^2 = 55%, p < 0.001). Subgroup analysis by interruption strategy is presented in Table 4. Omission of each of the potentially influential/outlier trials individually resulted in a loss of overall statistical significance and reduced the observed effect (WMD = -1.6 mmHg, p = 0.069, and WMD = -1.55, p = 0.053). In the interests of rigour, the analysis was repeated with the omission of both trials, resulting in a non-significant difference between interrupted and uninterrupted sitting conditions (WMD = -0.6 mmHg, 95% CI: -2.0 to 0.7, p = 0.359, SMD = 0.06, I^2 = 0%). Subgroup analysis by interruption strategy was repeated with the omission of the influential trials (Table 4). Due to the limited number of trials available, a meta-analysis assessing MAP responses to interrupted sitting was not performed.

Table 3 Meta-analysis of the effect of interrupted sitting on systolic blood pressure with and without influential trials. Subgroup analysis by sitting interruption strategy

	Pooled Effect					Heterogeneity			Asymmetry		
	WMD	LCI	UCI	P Value	SMD	Q	P Value	I^2	LFK	Quality	Trials
All	-4.43	-7.37	-1.49	0.003	-0.26	100.7	<0.001	70	-0.44	8	31
Interruption Strategy											
Aerobic	-5.21	-8.86	-1.55		-0.33	46.5	<0.001	63		8	18
SRA	-6.58	-15.7	2.54		-0.33	39.0	<0.001	87		9	6
Stand	-0.15	-3.31	3.01		-0.02	5.57	0.47	0		8	7
Analysis excluding influential trials											
All	-1.61	-3.20	-0.01	0.049	-0.14	15.5	0.97	0	-0.72	8	29
Interruption Strategy											
Aerobic	-2.66	-4.83	-0.49		-0.22	6.65	0.98	0		8	17
SRA	-0.63	-4.18	2.92		-0.06	1.26	0.87	0		9	5
Stand	-0.15	-3.31	3.01		-0.02	5.57	0.47	0		8	7

Abbreviations: WMD, weighted mean difference; LCI, lower confidence interval; UCI, upper confidence interval; SMD, standardised mean difference; LFK, Luis Furuya-Kanamori Index; SRA; simple resistance activities; N/A, not applicable. SMD: Trivial, small, moderate and large effect sizes are defined as <0.2, 0.2, 0.5, and 0.8 respectively. LFK: <±1 indicates no asymmetry, ±1 to ±2 suggests minor asymmetry, and >±2 indicates major asymmetry. I2: 25%, 50%, and 75% represent low, moderate, and high heterogeneity respectively. Quality is median quality score of included trials assessed using Heyland Methodological Quality Score, with a maximum score of 9.

Table 4 Meta-analysis of the effect of interrupted sitting on diastolic blood pressure with and without influential trials. Subgroup analysis by sitting interruption strategy

	Pooled Effect					Heterogeneity			Asymmetry		
	WMD	LCI	UCI	P Value	SMD	Q	P Value	I^2	LFK	Quality	Trials
All	-2.40	-4.45	-0.34	0.022	-0.19	57.4	<0.001	55	0.93	8	27
Interruption Strategy											
Aerobic	-1.97	-4.20	0.26		-0.17	28.0	0.03	43		8	17
SRA	-4.46	-11.0	2.1		-0.39	24.52	<0.001	84		9	5
Stand	0.12	-3.82	4.07		0.02	0.30	0.99	0		8	5
Analysis excluding influential trials											
All	-0.63	-1.98	0.72	0.359	-0.06	11.2	0.99	0		8	25
Interruption Strategy											
Aerobic	-0.64	-2.30	1.02		-0.06	6.82	0.96	0		8	16
SRA	-1.01	-4.39	2.36		-0.11	3.88	0.27	23		9	4
Stand	0.12	-3.82	4.07		0.02	0.30	0.99	0		8	5

Abbreviations: WMD, weighted mean difference; LCI, lower confidence interval; UCI, upper confidence interval; SMD, standardised mean difference; LFK, Luis Furuya-Kanamori Index; SRA, simple resistance activities; N/A, not applicable. SMD: Trivial, small, moderate and large effect sizes are defined as <0.2, 0.2, 0.5, and 0.8 respectively. LFK: <±1 indicates no asymmetry, ±1 to ±2 suggests minor asymmetry, and >±2 indicates major asymmetry. I2: 25%, 50%, and 75% represent low, moderate, and high heterogeneity respectively. Quality is median quality score of included trials assessed using Heyland Methodological Quality Score, with a maximum score of 9.

4. DISCUSSION

The aim of this meta-analysis was to consolidate the existing data relating to the effect of prolonged sitting (>1 hr), with and without interruption, on peripheral blood pressure in adults. The main findings were that; (1) prolonged uninterrupted sitting resulted in significant small and trivial increases in SBP and MAP, respectively particularly in younger age groups, whereas DBP was unaffected; and (2) regular interruptions to sitting may confer a protective effect against increases in SBP, particularly when aerobic interruption strategies are employed.

4.1 Limitations

Whilst the results of this meta-analysis provide novel insights, in order to fully contextualise the results, several potential limitations should be recognised. Firstly, there is a possibility of incongruency between trials utilising different methods of assessing peripheral blood pressure. Most trials utilised discrete oscillometric devices, whereas a limited subgroup utilised a mixture of ambulatory oscillometric [22,55] and photoplethysmography techniques [10,17,18]. Multiple reviews suggest that discrete and ambulatory pressure measurements can differ when implemented in a clinical setting [74–76]. However, in the interests of capturing all available data, trials utilising varying modes of peripheral blood pressure assessment were included with subgroup analysis performed to explore any differences. These subgroup analyses (Electronic Supplementary Material Appendix S7) revealed that studies utilising continuous blood pressure measures typically reported higher values for MAP and SBP, but this did not explain any excess significant heterogeneity. A further limitation of this analysis was the inability to effectively explore how sitting duration may influence the observed results. Currently it is unknown how sitting duration affects sitting-induced dysfunction, however, it was not possible to properly investigate this within this analysis given that trials employing longer sitting periods (> 4 hours [median split]) typically recruited older samples than trials utilising shorter sitting periods ($\leq$ 4 hours) (48.7 years vs 27.9 years, respectively). Another potential limitation is the use of tightly controlled periods of prolonged uninterrupted sitting as a comparison for objective (2). Extended periods of uninterrupted sitting may lack external validity and provide an unfair comparison producing inflated results in favour of interrupting sitting. Of note, it is important to acknowledge the potential confounding effect of diurnal variations in blood pressure whereby blood pressure typically increases from the early hours of the morning until the early afternoon [77,78]. Diurnal variation is influenced by both intrinsic and extrinsic factors and whilst intrinsic factors are important, evidence suggests that extrinsic factors may be more influential [79,80]. Importantly, most studies in this analysis controlled for extrinsic factors known

to affect diurnal variations in blood pressure, specifically food, alcohol, and caffeine intake, and physical activity, prior to experimental visits. Encouragingly, the results from objective (2) suggest that the observed increases in blood pressure are avoidable and thus still lend evidence in support of regularly interrupting bouts of prolonged sitting. Finally, only two studies performed *a priori* power calculations with peripheral blood pressure as the primary outcome measure [22,55]. Of these two studies, only one was suitably powered following participant dropout and instrument malfunction [22]. To this end, it is plausible that many of the included trials were underpowered to detect the true effect of prolonged sitting, with and without interruption, on peripheral blood pressures. However, by conducting this meta-analysis, statistical power has been increased and an indication of the likely effect has been calculated.

4.2 Prolonged uninterrupted sitting

The results of this meta-analysis demonstrated that an acute bout of prolonged uninterrupted sitting resulted in small and trivial increases in MAP and SBP, respectively. Conversely DBP appears to be relatively unaffected by an acute bout of prolonged uninterrupted sitting, showing no significant change. The increases in MAP and SBP are likely mediated by a complex interaction of mechanisms. One such mechanism may be a consequence of the increased blood pooling observed in the lower limbs during sitting [11,18,19,69,81–84]. This would induce a reduction in venous return, which has been suggested to decrease renal perfusion pressure, stimulating the renin-angiotensin aldosterone system (RAAS), ultimately driving an increase in blood pressure [82,85]. Total peripheral resistance, a key moderator of blood pressure, may also increase due to localised endothelial dysfunction in lower-limb arteries [4] and a concomitant increase in stiffness and vascular tone [86–88], again elevating blood pressure. Whilst the intrinsic co-dependency of blood pressure and arterial stiffness prevent the identification of the primary antecedent, it is also conceivable that observed increases in central [9,11,69] and peripheral arterial stiffness may augment pulse wave propagation throughout the arterial tree causing a transient increase in SBP [89,90]. The reasons for the lack of change in DBP are unclear. The major determinants of changes in DBP are arterial compliance and total peripheral resistance [91]. It is possible that the trivial to small changes in arterial stiffness (and thus compliance) and total peripheral resistance observed in previous studies are not sufficient to significantly influence DBP but may of sufficient magnitude to explain the trivial to small increases in SBP and MAP observed in this analysis.

Age-related structural changes in elastic arteries and the subsequent concomitant alterations to peripheral blood pressure may help to explain the observed differences in MAP and SBP responses to sitting across age groups

(Table 2). It is understood that with increasing age, there is typically a concomitant increase in aortic stiffness which is associated with increased resting SBP [37], thus the small-moderate insult posed by prolonged sitting may be masked by already elevated resting values. Additionally, the lack of a detrimental response with increasing age may be the result of diminished RAAS activity which is associated with increased age [38,92,93]. Age-related differences may also be explained in part by differences in the habitual physical activity of samples. Typically, trials that recruited middle-aged (45-64 years) and aged (65-79 years) participants, appear to have purposefully recruited more sedentary individuals and excluded those who were physically active [13,21,65–67]. In contrast, trials involving young adults, aged between 18-24 years, typically reported that participants were healthy and recreationally active [12,16,18,19,73]. Currently, there are limited and conflicting data exploring the effect of habitual physical activity and fitness on the cardiovascular responses to prolonged uninterrupted sitting. Of the two articles that have assessed the effect of fitness status on sitting-induced vascular dysfunction, neither identified statistically-significant differences in MAP between groups [12,15]. However, it should be noted that as MAP was not the primary outcome, these studies may not have been adequately powered to detect significant changes in peripheral blood pressure. Nonetheless, future research should aim to understand the potential confounding effect of habitual physical activity on sitting-induced changes to the vascular system.

4.3 Sitting Interruption

Due to the limited number of trials assessing MAP responses to interrupted sitting, meta-analysis was only performed for SBP and DBP. Meta-analysis of DBP demonstrated a trivial significant decrease (beneficial) when sitting was interrupted compared to control (WMD = -2.4~~0~~ mmHg, 95% CI: -4.4~~5~~ to -0.3~~4~~, SMD = -0.19), however, sensitivity analysis showed that two trials from one study [58] unduly influenced this result and that the removal of either resulted in a loss of overall statistical significance. The reason for this undue influence is unclear. However, it may be the case that the novel sample, i.e., participants with the highest BMI (33 ± 3.4 kg.m^2) and type 2 diabetes mellitus, influenced the results. Regardless, due to the limited robustness of this analysis, any inferences about DBP responses to bouts of interrupted prolonged sitting should be made with caution. The same trials were also deemed to unduly influence the meta-analysis of SBP responses to interrupted sitting, however, sensitivity analysis suggests that the overall effect is more robust. Analysis of 31 trials, including two potentially influential trials from one study [58], demonstrated a small significant beneficial effect on SBP when prolonged sitting was interrupted (WMD = -4.4 mmHg, 95% CI: -7.4 to -1.5, SMD = -0.26). Re-analysis of 29 trials, omitting influential trials, revealed a significant trivial beneficial effect on SBP (WMD = -1.6 mmHg, 95% CI: -3.2 to -0.01, SMD = -0.14).

Subgroup analysis was conducted to investigate whether an optimum interruption strategy existed. As shown in Table 3, aerobic interruption strategies produced a significant small effect for SBP in both models, with and without influential trials. Conversely, simple resistance activities and standing breaks produced non-significant small and trivial effects respectively, with both becoming trivial in the model omitting influential trials (Table 3). It should be noted, however, that both the simple resistance activities and standing breaks subgroups consisted of far fewer trials compared to the aerobic interruption strategy subgroup. Thusly, further research is needed before firm conclusions can be made regarding the efficacy of either simple resistance activities or standing breaks as sitting interruption strategies.

The varying efficacy of different interruption strategies may be due to differences in the circulatory stimulus each type of intervention created. The majority of aerobic interruption strategies consisted of walking or running breaks [13,20,22,55,58,60,63,65–67], and three trials implemented cycling interruptions [22,59,62]. Within the aerobic interruption strategy subgroup, the greatest differences in SBP between control and experimental conditions were observed in trials that typically used longer ($\geq$ 5 minutes) [55,66], more frequent [13,20], or higher intensity interruption strategies [55]. Conversely, trials that implemented shorter interruptions ($\leq$ 5 minutes) typically showed more trivial effects [55,67]. Longer interruptions or those of a higher intensity are likely to result in a greater mechanical "muscle pump" in the lower limbs, promoting venous return [94,95], potentially offsetting the blood pooling associated with prolonged sitting. In turn, this may prevent the previously discussed activation of the RAAS and therefore avert increases in blood pressure. Alternatively, it is conceivable that longer bouts, particularly the 30 minutes of moderate intensity exercise implemented by one trial [55], may result in transient post-exercise hypotension [94,95]. Previous work has demonstrated that frequent short bouts of exercise (3 x 10 minutes) can result in similar or indeed greater transient reductions in SBP compared to longer exercise bouts of the same intensity [96,97]. Whilst none of the frequent interruption strategies investigated in this analysis were as long as 10 minutes, it is conceivable that differing magnitudes of post-exercise hypotension may explain the greater effect of longer interruption strategies.

4.4 Implications

Prior to this meta-analysis, mounting evidence suggested that bouts of prolonged uninterrupted sitting may negatively impact markers of cardiometabolic and vascular health. However, one important, and easily measurable metric of cardiovascular health, peripheral blood pressure, was yet to be reviewed and meta-analysed. As a result, it was unclear to what degree bouts of prolonged uninterrupted sitting affected peripheral blood pressure in adults

and whether regular interruption strategies may prevent any deleterious effects. Additionally, while sedentary behaviours such as prolonged sitting are common across age demographics, it was not known whether age-associated changes in cardiovascular physiology may influence sitting-induced responses. This review found that bouts of prolonged sitting resulted in a small but significant increase in MAP driven by an increase in SBP. Additionally, it appears that interrupting prolonged sitting, particularly with aerobic interruption strategies, may confer some protective effect. In order to provide useful public health guidelines, advice should centre on the FITT principle (frequency, intensity, time, and type). It appears that aerobic interruption strategies (type) confer the most reliable protective effect against the deleterious effects of sitting. Consequently, future research should aim to identify optimum frequency, intensity, and timings of interruptions.

5. CONCLUSIONS

Existing epidemiological research has highlighted an association between sedentary behaviours, such as prolonged sitting, and CVD incidence and all-cause mortality. Subsequent research has identified that bouts of prolonged sitting negatively impact a number of cardiometabolic outcomes, including peripheral blood pressure. Repeated acute increases in blood pressure may expose the vascular system and critical end-organs to excessive stress. Thus, understanding the implications of blood pressure responses to bouts of prolonged sitting is prudent. This meta-analysis is the first to consolidate the existing data regarding peripheral blood pressure responses to prolonged uninterrupted and interrupted sitting. The results of this analysis show that (1) acute bouts of prolonged sitting ($\geq$ 1 hr) result in statistically significant increases in MAP and SBP, but not DBP, particularly in young individuals, and that, (2) interrupting sitting, especially with aerobic interruption strategies such as walking breaks, may prevent these deleterious effects. Future research should aim to identify optimal frequencies, intensities, and timings of sitting interruption strategies.

Data Availability

The data analysed for this meta-analysis are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

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TABLE LEGENDS

ELECTRONIC SUPPLEMENTARY MATERIAL

Electronic Supplementary Material Appendix S1 Key words for literature search

Electronic Supplementary Material Appendix S2 Forest plot for meta-analysis of the effect of uninterrupted sitting on systolic blood pressure

Electronic Supplementary Material Appendix S3 Forest plot for meta-analysis of the effect of uninterrupted sitting on diastolic blood pressure

Electronic Supplementary Material Appendix S4 Forest plot for meta-analysis of the effect of uninterrupted sitting on mean arterial pressure

Electronic Supplementary Material Appendix S5 Forest plot for meta-analysis of the effect of interrupted sitting on systolic blood pressure

Electronic Supplementary Material Appendix S6 Forest plot for meta-analysis of the effect of interrupted sitting on diastolic blood pressure

Electronic Supplementary Material Appendix S7 Subgroup analysis of mean arterial pressure, systolic, and diastolic blood pressure by assessment type