



Review

Time of the day of exercise impact on cardiovascular disease risk factors in adults: a systematic review and meta-analysis

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ABSTRACT

Objectives: To compare the effect of a single bout of morning vs. evening exercise on cardiovascular risk factors in adults.

Design: Systematic review and meta-analysis.

Methods: A systematic search of studies was conducted using PubMed and Web of Science from inception to June 2022. Selected studies accomplished the following criteria: crossover design, acute effect of exercise, blood pressure, blood glucose, and/or blood lipids as the study's endpoint, a washout period of at least 24 h, and adults. Meta-analysis was performed by analyzing: 1) separated effect of morning and evening exercise (pre vs. post); and 2) comparison between morning and evening exercise.

Results: A total of 11 studies were included for systolic and diastolic blood pressure and 10 studies for blood glucose. Meta-analysis revealed no significant difference between morning vs. evening exercise for systolic blood pressure ($g \Delta = 0.02$), diastolic blood pressure ($g \Delta = 0.01$), or blood glucose ($g \Delta = 0.15$). Analysis of moderator variables (age, BMI, sex, health status, intensity and duration of exercise, and hour within the morning or evening) showed no significant morning vs. evening effect.

Conclusions: Overall, we found no influence of the time of the day on the acute effect of exercise on blood pressure neither on blood glucose.

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Practical implications

A single bout of exercise causes a short-term decrease in systolic blood pressure independently of the time of the day.

A single bout of exercise produces a short-term increase in blood glucose independently of the time of the day.

We cannot make robust conclusions since the available literature is heterogenous and of frequent unclear methodological quality.

1. Introduction

Mammalian cells possess an internal molecular clock that controls metabolic processes through the so-called “clock genes”, regulated in a transcriptional-translational feedback loop.¹ This feedback loop consists of an autonomous central clock placed in the suprachiasmatic

nucleus of the hypothalamus that, affected by endogenous and external cues (e.g., exercise), regulates peripheral clocks.² In animal models, the alteration of the molecular clock has been associated with the occurrence of obesity and type II diabetes mellitus.³ Similarly, in humans, shifted sleep patterns seem to interfere with several metabolic pathways.⁴ Shifted working, short sleep duration, exposure to artificial light, inadequate eating time window, and lack of physical activity, are some characteristics of the modern lifestyle that contributes to the occurrence and worsening of cardiovascular disease (CVD).⁵

Exercise is a well-known protective factor against CVD and can reduce all-cause mortality by 50%.⁶ Recent epidemiological studies highlight the relevance of the time of exercise on its cardiovascular and metabolic effects^{7–9}. To understand these adaptations, it is of interest to define the physiological acute response to exercise at different times of the day. Savikj et al.¹⁰ reported that a single bout of evening high-intensity exercise was more efficacious at improving blood glucose in men with type 2 diabetes than morning exercise (although they did not control previous diet). Jones et al.^{11,12} found that the acute hypotensive effect of exercise was more significant in the evening compared to

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morning in normotensive men. In contrast, Brito et al.¹³ found a greater hypotensive effect of morning than evening exercise in pre-hypertensive men. Given the current contradiction would be of great interest to systematically review the literature and synthesize the results with a standardized protocol (i.e., meta-analysis) to respond whether exercise has a different impact on CVD risk factors when performed during the morning or the evening. This finding would be of clinical and public health interest contributing to optimize the effects of exercise in the prevention of CVD. Thus, the objective of this systematic review and meta-analysis is to analyze the time of the day of exercise-induced effects on CVD risk factors in adults.

2. Methods

To follow the quality of the design, implementation, and reporting of this meta-analysis, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁴ (see Table S1) and relevant methodological references^{15–17} throughout the entire process.

2.1. Search strategy and information sources

We performed a systematic search of studies in PubMed and Web of Science databases, from inception to June 2022. We used the following terms for that purpose: exercise, time of day, diurnal variation, circadian rhythm, morning, afternoon, evening, glucose, triglycerides, blood lipids, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, blood pressure with synonymous and truncation operators adapted to each database (see Table S2 for specific search strategies).

2.2. Eligibility criteria

Studies were eligible to be included upon meeting the following criteria: (a) crossover design studies investigating the effect of morning vs. evening exercise; (b) to include at least one cardiovascular risk factor as a study's endpoint (i.e., blood glucose, blood pressure, total cholesterol, HDL, LDL, or triglycerides); (c) to investigate the acute effect of exercise before and in between 15 to 60 min; (d) to consider a washout period of at least 24 h between exercise sessions; (e) to include adults above 18 years old regardless of their health or physical condition; (f) manuscripts written in English or Spanish; (h) to provide statistical indicators that allow calculating the effect size; and (j) not to include any type of drug, dietary supplement or equipment before exercising that could affect exercise effects.

2.3. Selection and data collection process

Based on the selection criteria, screening by title and abstract was independently performed by two authors (R.S.L. and F.A.G.) using End-Note. Disagreements between authors were resolved by discussion and, if needed, a third author's (J.R.R.) final decision was required. Full manuscripts of potential studies were obtained and screened for final inclusion and data extraction following the same procedure. Data extraction of the included studies was performed through a codebook and a coding protocol previously created for this purpose in a standardized form. The standardized form included the authors' names, and year of publication (extrinsic variables); participants and treatment characteristics (substantive variables); and methodological variables, in addition to the study outcomes. We contacted the authors of studies when required data of their works were not explicitly found. Outcomes of interest were systolic (SBP), diastolic (DBP) and mean blood pressure (MBP), blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. We extracted data from pre and 15 to 60 min post-exercise at both moments of the day (morning and evening). If a study had several points of measurements post-exercise, data closer to

60 min post were selected. We discarded data coming from immediately post-exercise measurements because exercise is a stressor that acutely elevates blood glucose and blood pressure while occurring,^{18,19} and could mask the cardiovascular benefits coming later. Exercise performed from wake up to 12:00 was considered "morning exercise", and the one performed from 14:00 to bedtime was considered "evening exercise". If a study was designed with several morning and/or evening trials (e.g., 8:00 vs. 12:00 vs. 15:00 vs. 18:00), we chose for morning the one closer to 8:00 and for evening, the one closer to 18:00. These were the most common exercise times in the included studies and we decided to harmonize the data as much as possible. Lastly, if the same data/study was used in different original articles for different purposes, only the report that provides more detailed information on the subject of this systematic review-meta-analysis was included.

2.4. Study risk of bias assessment

Included studies were assessed for crossover design methodological quality using relevant items, based on the Cochrane handbook and expert comments.²⁰ Nine standard items were used to evaluate the risk of bias: 1) to follow an appropriate cross-over design; 2) to randomize the order of receiving treatment; 3) to account for the carry-over effects; 4) participants blinding (this was always considered as low risk of bias since morning and evening conditions cannot be blinded); 5) to apply blinding methods to researchers; 6) if an appropriate statistical analysis was performed; 7) to provide information about incomplete outcome data; 8) to avoid selective outcome reporting; and 9) to measure outcomes appropriately (i.e., to control previous conditions to exercise: physical activity, fasting hours and diet). All of them were judged as high, unclear, or low risk of bias based on the study methods reported in the original articles.

2.5. Effect measures and synthesis methods

We calculated two effect sizes: 1) separated effect of morning and evening exercise (pre vs. post); and 2) comparison between morning and evening exercise. To compare the separated effect of exercise during both morning and evening, we followed the approach by Kebede et al.²¹ First, we calculated Cohen's *d* for repeated measures (Cohen's d_{RM}) taking into consideration baseline imbalance and pre/post correlation.²² Pre/post correlations were computed from standard deviations (SD_{pre} and SD_{post}), and standard deviation values for change scores.²¹ Second, we calculated the Hedges' *g* for repeated measures since all of the studies included less than 20 participants.²² To compare morning and evening's effect sizes we used the formula reported by Madeyski et al.²³ Standard errors of the effect sizes presented in the forest plot were calculated from the variance following previously published formulas.²⁴ Table S3 summarizes the equations used to calculate the effect sizes. The effect sizes can be interpreted according to the standard benchmarks: values around 0.2 are considered a small effect size, 0.5 is considered a medium effect, and above 0.8 is considered a large effect size.²⁵ Using R software, the random-effect model of the inverse variance method was used to calculate the pooled Hedges' *g* and the corresponding 95% CI. Heterogeneity was assessed with the Higgins I^2 statistic and P values, being classified as not important (0%–40%), moderate (30%–50%), substantial (50%–75%), or considerable (75%–100%).²⁶

We also performed a sensitivity analysis to determine whether potential moderators are influencing the effect sizes. For that purpose, we used meta-regression analyses for continuous variables and analyses of variance for the categorical variables. The moderators included were sex, BMI, age, health status (i.e., healthy and unhealthy), hour in the morning, hour in the evening, duration of exercise, and intensity (i.e., low to moderate and moderate to high) of exercise. Moderation of the hour within the morning and the hour within the evening were only possible to be analyzed from the separate meta-analyses of

morning and evening exercise. Potential publication bias was assessed using Egger's test and the Rosenthal method (fail-safe N index).

3. Results

3.1. Search results

The systematic search yielded 1273 studies. After removal of duplicates and screening by title and abstract, 177 eligible full-text documents were evaluated for inclusion in the meta-analysis. The flowchart of the search and selection of studies is shown in Fig. 1. A total of 28 crossover studies^{10,11,33–42,44,46–50,52,53,33,35–39} were selected for inclusion. Of those, 6 were excluded because they did not provide statistical data to calculate effect size or full text was not available. Thus, a total of 22 studies were finally included in the meta-analysis.

3.2. Studies characteristics

The general characteristics of all included studies are summarized in Table 1. For SBP and DBP, the total sample was composed of 144 participants (9.03% women), the median age was of 29 years ($Q_1 = 22.3$, $Q_2 = 29$, $Q_3 = 49$), and the mean body mass index (BMI) was $25.95 \text{ kg/m}^2 \pm 3.62$. Most of the study's participants were healthy (61.11%), being the rest hypertensives (27.78%) or pre-hypertensives (11.11%). For MBP, the total sample was composed of 103 participants, 0% women, with a median age of 29 years ($Q_1 = 26$, $Q_2 = 29$, $Q_3 = 49$) and a BMI of $26.38 \pm 3.32 \text{ kg/m}^2$. Most of the participants were healthy (56.31%), the others were hypertensives (28.16%) or pre-hypertensives (15.53%). Regarding blood glucose, the total sample was composed of 91 participants, 27.47% women, with a median age of 30.5 years ($Q_1 = 25$, $Q_2 = 30.5$, $Q_3 = 49$) and a mean BMI of $25.61 \pm 1.93 \text{ kg/m}^2$. Part of the participants was healthy (42.86%) or had no metabolic disease, i.e., mild sleep apnea (13.19%),⁴⁴ the others presented type 1 or type 2 diabetes (43.96%). with regard to blood lipids, we did not find enough studies to meta-analyze this outcome: only 1 of the studies met the inclusion criteria determining blood triglycerides.³³

Considering the total of the included studies, most of them were originally from the United Kingdom ($n = 6$), the United States of America ($n = 4$), and Brazil ($n = 3$); the others were conducted in Australia, Canada, Italy, Japan, Sweden, Tunisia, and Turkey. Exercise interventions were mainly aerobic exercise sessions ($n = 19$)^{10,11,40,42–44,46–48,51,52,12,13,33,35–39}; the rest applied strength training ($n = 2$)^{41,49} or combined strength and aerobic exercise ($n = 1$)³⁴; exercise sessions had a mean duration of 27.25 ± 15.03 min. Respectively, median morning and evening hours for SBP and DBP were 8:00 a.m. (min = 7:00, max = 9:00 a.m.) and 6:00 p.m. (min = 4:00, max = 8:00 p.m.). For blood glucose, median hours were 7:00 a.m. (min = 6:00, max = 8:00 a.m.) and 4:00 p.m. (min = 3:00, max 7:00 p.m.). Outcomes were evaluated at rest previous to exercise and post-exercise within a period of 15 to 60 min.

3.3. Acute effect of morning vs. evening exercise on cardiovascular disease risk factors

Meta-analysis of the acute effect of the time of day of exercise on SPB (11 studies), DBP (11 studies), and blood glucose (10 studies) are shown in Fig. 2. Meta-analysis of the acute effect of the time of day of exercise on MPB (6 studies) is shown in Fig. S3. We found no significant differences in the morning vs. evening effect of exercise on SBP (Hedges' $g \Delta$: 0.02 favor morning [$-0.22, 0.26$]; $p = 0.88$), DBP (Hedges' $g \Delta$: 0.01 favor morning [$-0.26, 0.23$]; $p = 0.95$) or blood glucose (Hedges' $g \Delta$: 0.15 [$-0.22, 0.53$]; $p = 0.42$). Mean changes expressed in mmHg and mmol/L are reported in Table 2. Heterogeneity was low for SBP and DBP ($I^2 \leq 21.42\%$, $p > 0.05$), and moderate for blood glucose ($I^2 = 34.73\%$, $p = 0.13$).

Blood lipids could not be meta-analyzed because only one study was reporting this outcome. Aldemir et al.³³ explored the diurnal variation of the effect of exercise on blood lipids, specifically on triglycerides. They reported that triglycerides levels 30 min after evening exercise were significantly lower from baseline (from 20.07 ± 5.08 to $15.52 \pm 4.41 \text{ UI/l}$) but not after morning exercise (from 22.61 ± 7.49 to $20.20 \pm 6.29 \text{ UI/l}$).

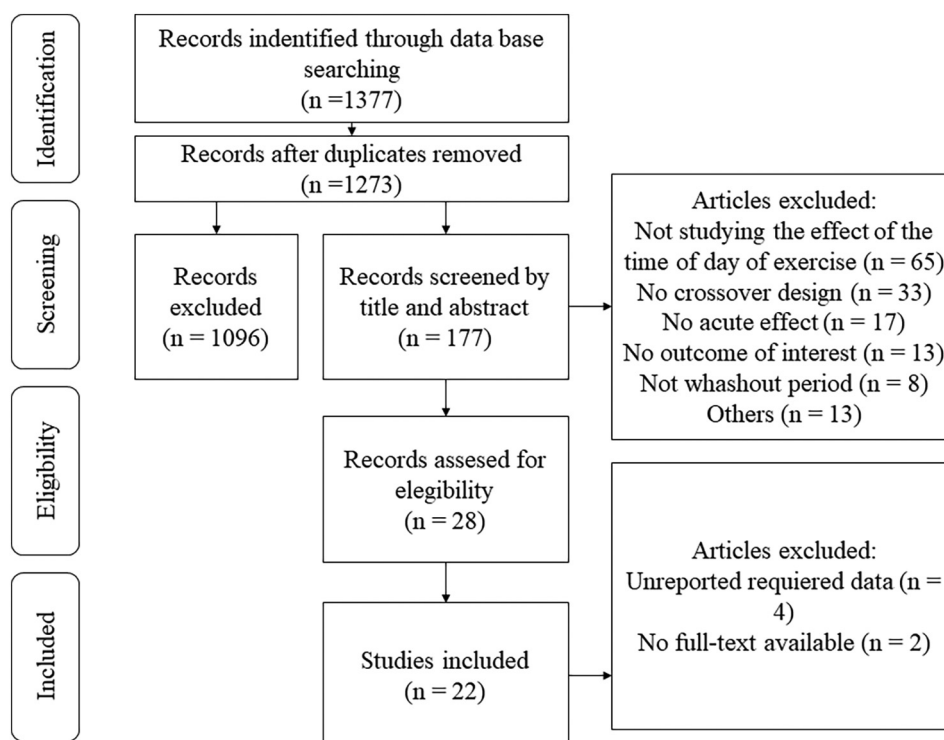


Fig. 1. Flowchart of the search and selection of studies.

Table 1
Overview of acute effect of time of day of exercise studies on CVD risk factors.

Acute effect of time of day of exercise on systolic, diastolic and mean blood pressure													
Study	N (sex:)	Age (SD)	BMI (SD)	Chrono-type	Health and training status	Medication	Design	Exercise intervention	Previous conditions	Time of the day	Main outcome	Minutes post exercise	Main findings
Aldemir and Kilic, 2005	10 (male)	27 (1.6)	23.9 (0.7)	Not reported	Healthy, moderately active	No	Randomized crossover	Submaximal exercise test: 1 bout × 30 min on cycle ergometer (intensity: 70% VO2max)	Diet, fasting, or previous activity not reported	07:30 vs 17:30	Mean blood pressure Blood triglycerides	30	Although blood pressure decreased in response to submaximal exercise, there was no time of day differences neither at baseline, post-exercise nor recovery. Blood triglycerides decreased after evening exercise but not after morning exercise.
Azevedo et al., 2017	11 (female)	57 (5.1)	30.7 (3.9)	Not reported	Hypertension, training status not reported	anti-hypertensive treatment	Randomized crossover with control condition	Strength training: 8 maximum repetitions test: (1 × 10 repetitions at 50% load) + Moderate-to-severe cycling for 20 min at 7–8 SPE scale	Diet, fasting, or previous activity not reported. Caffeine intake was not suspended	8:00 vs 18:00	Systolic and diastolic blood pressure	60	No differences were observed for post-exercise hypotension between morning and evening exercise. Diastolic blood pressure did not show reductions after exercise.
Boukella et al., 2018	12 (male)	33 (5)	21.9 (1.2)	Not reported	Healthy, athletes	No	Randomized crossover	10 km treadmill time trial (controlled environmental conditions: 28 °C, 70% relative humidity) Intensity not reported	Diet, fasting, or previous activity not reported	9:00 vs 18:00	Systolic and diastolic blood pressure	60	No differences were found in mean blood pressure reduction after exercise between the morning and the evening trial.
Bousseta et al., 2017	11 (male)	21.82 (0.5)	23.4 (1.3)	Not reported	Healthy, trained	No	Randomized crossover	Yo-Yo tests level 1: 20-m shuttle runs at increasing velocities until exhaustion.	Not controlling previous diet, but standardized fasting conditions (at least 6 h). Inactivity the day before.	8:00 vs 18:00	Systolic and diastolic blood pressure	60	No differences were found in systolic or diastolic blood pressure reduction after exercise between the morning and the evening trial. Systolic blood pressure was higher in the polluted area at both times of day.
Brito et al., 2015	16 (male)	32.0 (7.0)	28.9 (2.8)	Intermediate types	Pre-hypertension. Sedentary to moderately active.	No	Randomized crossover with control condition	1 bout × 45 min on cycle ergometer (intensity: 50% VO2peak)	Standardized diet, standardized previous fasting (0.5 h). Inactivity the day before.	09:00 vs 18:30	Systolic, diastolic and mean blood pressure	45	Morning aerobic exercise had an important and greater hypotensive effect than evening exercise
Brito et al., 2020	14 (male) for ACEi, 15 (male) for ARB	50 (8) for ACEi, 49 (8) for ARB	30.9 (3.6) for ACEi, 29.8 (4.1) for ARB	Intermediate types	Hypertension. Sedentary	Group 1: angiotensin-converting enzyme inhibitors (ACEi) Group 2: angiotensin II receptor blockers (ARB)	Randomized crossover	Maximal cardiopulmonary exercise test on cycle ergometer (increasing workload 15 W every minute until exhaustion).	Abstain from caffeine and alcohol the day before. standardized previous fasting (2 h). Inactivity the day before.	8:00 vs 21:00	Systolic, diastolic and mean blood pressure	30	Exercise produced bigger hypotensive effect after evening exercise compared to morning in hypertensives receiving anti-hypertensive drug

Chan-Dewar et al., 2012	10 (male n = 10, female n = 2)	24 (3)	23.5 (1.2)	Not reported	Healthy, trained	No	Randomized crossover	40 km cycling on a computerized cycle training system (intensity: 90–100% lactate threshold, 74–90% HRmax)	Standardized previous diet and fasting (1.5 h). Inactivity the day before.	8:00 vs 18:00	Systolic and diastolic blood pressure	60	can influence the diurnal variation of post-exercise hypotension. No differences were found in systolic or diastolic blood pressure reduction after a high-intense exercise between the morning and the evening trial. During exercise in the early evening there was a trend to decrease for diastolic blood pressure compared to morning. But there was no difference for systolic blood pressure.
Di Blasio et al., 2010	28 (male)	25 (2)	24.2 (1.72)	Not reported	Healthy, sedentary	No	Randomized crossover	1 bout of cycling on cycle ergometer (intensity: 10 min. at 55% HRmax, 35 min. at 70% HRmax, 5 min. Cool down)	Abstain from caffeine and alcohol the day before, standardized previous fasting conditions (3 h). No information about activity the day before.	9:00 vs 14:00 vs 18:30	Mean blood pressure	30	Only diastolic blood pressure decreased 15 min after exercise, but there were no differences in the response relative to the time of day.
Focht et al., 2009	21 (male)	21.4 (2.5)	Not reported	Mixed	Healthy, recreationally active	Not reported	Randomized crossover	45 min of strength training: 4 exercises completed for 3 sets of 10 repetitions at 75% 1 RM	Abstain from caffeine and alcohol the day before. Not report information about fasting conditions. Inactivity the day before.	7:00 vs 19:00	Systolic and diastolic blood pressure	15	Only diastolic blood pressure decreased 15 min after exercise, but there were no differences in the response relative to the time of day.
Jones et al., 2008	12 (male)	26.0 (5.0)	23.5 (0.7)	Not reported	Healthy, recreationally active	No	Randomized crossover	30 min cycling on cycle ergometer (intensity: 70% VO2peak)	Abstain from caffeine and alcohol the day before, standardized previous fasting conditions (4 h). Inactivity the day before.	08:00 vs 16:00	Systolic, diastolic and mean blood pressure	20	Afternoon aerobic exercise produced a bigger hypotensive effect than morning exercise.
Jones et al., 2009	8 (male)	29.0 (7.0)	26.6 (9.5)	Not reported	Healthy, recreationally active	No	Randomized crossover	Continuous steady-state: 30 min cycling on cycle ergometer (intensity: 70% VO2peak) Intermittent steady-state: 3 bouts of 10 min cycling on cycle ergometer separated by 10 min resting periods (intensity: 70% VO2peak)	Abstain from caffeine and alcohol the day before, standardized previous fasting conditions (4 h). Inactivity the day before.	08:00 vs 16:00	Systolic, diastolic and mean blood pressure	20	Afternoon aerobic exercise decreased greater mean and systolic blood pressure compared to morning exercise. This diurnal variation was less marked following intermittent than continuous exercise.

(continued on next page)

Table 1 (continued)

Study	N (sex:)	Age (SD)	BMI (SD)	Chrono-type	Health and training status	Medication	Design	Exercise intervention	Previous conditions	Time of the day	Main outcome	Minutes post exercise	Main findings
Acute effect of time of day of exercise on systolic, diastolic and mean blood pressure													
O'Connor et al., 1992	12 (male)	22.3 (2.7)	23.3 (0.1)	Mixed but not definitively morning or evening types	Not reported	Not reported	Randomized crossover	Submaximal exercise test: 20 min running on treadmill (intensity: 70% VO2max)	Not reported	8:00 vs 16:00 vs 20:00	Systolic and diastolic blood pressure	20	Post-exercise hypotension was independent of the time of the day that exercise was performed.
Acute effect of time of day of exercise on blood glucose													
Fernandes et al., 2014	9 (male)	31 (7.3)	23.8 (1.7)	Intermediate (n = 5) or moderate morning (n = 4)	Healthy, trained	Not reported	Randomized crossover	1000-m cycling time trial in the shortest time possible	Standardized diet and previous fasting (6 h). Inactivity the day before.	08:00 vs 18:00	Blood glucose	60	Blood glucose showed a tendency to increase greater after morning exercise compared to evening, accompanied with a more exacerbated response to exercise of norepinephrine at the same time of the day. There were no differences for the blood glucose response to exercise between morning and evening trials.
Galliven et al., 1997	7 (female)	29 (2.6)	23.7 (4.5)	Not reported	Healthy, mixed training status	No	Randomized crossover	20 min running on treadmill (intensity: 5 min at 50% VO2max, 5 min at 90% VO2max)	Only abstain from caffeine and alcohol the day before, standardized fasting (6 h). Inactivity the day before	07:00 vs 15:00	Blood glucose	60	There were no differences for the blood glucose response to exercise between morning and evening trials.
Hobson et al., 2009	7 (male)	24.0 (2.0)	24.2 (3.1)	Not reported	Healthy, recreationally active	Not reported	Randomized crossover	1 bout of cycling on a cycle ergometer until exhaustion (intensity: 65% VO2max) Environmental conditions: 35.1 (0.4) °C and 60 (4) % relative humidity.	Standardized previous diet and fasting (6 h). Inactivity the day before	06:45 vs 18:45	Blood glucose	15	Blood glucose levels were not reduced after exercise, and there were no differences between morning and evening trials.
Larsen et al., 2019	11 (male)	49 (5)	28 (3)	Not reported	Mild sleep apnoea, sedentary	No	Randomized crossover	30 min HIIT (intensity: 60 work s at 100%VO2max, 240 s rest at 50% VO2peak)	Controlled previous diet, not standardized fasting conditions (overnight for morning, 3 h for evening). Abstain from alcohol and caffeine the day before,	6:00 vs 15:00 vs 19:00	Blood glucose	30	After morning exercise blood glucose showed bigger increase than after evening trials.
McIver et al., 2019	12 (male)	25.0 (3.0)	26.0 (4.0)	Intermediate	Healthy, recreationally active	No	Randomized crossover	45 min walking on treadmill (intensity: 55% VO2peak)	Abstain from alcohol and caffeine the day before,	08:00 vs 15:00	Blood glucose	30	There were no diurnal differences for blood glucose in response to exercise.

Munan et al., 2020	14 (male n = 8, female n = 6)	65 (9)	27.2 (3.5)	Not reported	Type 2 diabetes, sedentary	Not insulin or corticosteroids. Metformin (n = 12).	Randomized crossover	40 min walking on treadmill (intensity: 5 km/h with 0.5% grade)	Standardized previous fasting (8 h). Inactivity the day before. Standardized previous diet but not fasting (overnight for morning, 3 h for afternoon, 20 min for evening). Inactivity the day before.	Not reported	Blood glucose	30	The afternoon exercise condition had the largest decrease in blood glucose after exercise. No significant diurnal differences were found between trials in mean 24 h continuously monitored glucose.
Ruegger et al., 1990	6 (male n = 3, female n = 3)	30 (9.8)	Not reported	Not reported	Type 1 diabetes, recreationally active	Ultralente-based intensive insulin therapy	Randomized crossover with control condition	30 min cycling on cycle ergometer (intensity: 60% VO2max)	Standardized diet but not fasting hours (9 h for morning, 4 h for evening). No information about activity the day before.	7:00 vs 16:00	Blood glucose	60	Exercise in the morning produced a significant increase in blood glucose, while this hyperglycaemic effect was absent after evening exercise.
Savij et al., 2018	11 (male)	60 (2)	27.5 (0.6)	Not reported	Type 2 diabetes, sedentary	Dietary treatment or metformin	Randomized crossover	HIIT: 6 bouts × 1 min work (intensity > 220 W) + 1 min rest (minimal load).	No information about activity the day before.	08:00 vs 16:00	Blood glucose, HDL, triglycerides	60	Afternoon HIIT reduced blood glucose. Morning HIIT induced an increase of blood glucose. There was no time of day effect neither in HDL nor in triglycerides, measured before and after 2 weeks of exercise.
Tanaka et al., 2021	11 (male)	24.5 (2.8)	22.3 (1.1)	Not reported	Recreationally active	No	Randomized repeated measures	60 min cycling on cycle ergometer (intensity: 60% VO2max)	Standardized diet but not fasting hours (overnight fast for morning, 3 h for evening)	7:00 vs 16:00	Blood glucose	60	The effect of morning versus afternoon exercise was not significantly different during the 60 min period after the test. However, blood glucose increased greater after a given post-exercise meal in the morning compared to afternoon. Morning exercise led to an increase in blood glucose meanwhile afternoon exercise lead to a decrease.
Toghi-Eshghi et al., 2019	12 (male n = 3, female n = 9)	31.6 (8.9)	26.6 (3.8)	Not reported	Type 1 diabetes, recreationally active	Insulin pump (n = 8), insulin injections (n = 4)	Randomized crossover	43 min of strength training: 3 sets involving major muscle groups × 8 repetitions (intensity: 8 RM)	Controlled previous diet, not standardized fasting (overnight for morning, 3 h for evening). Inactivity the day before.	07:00 vs 17:00	Blood glucose	60	

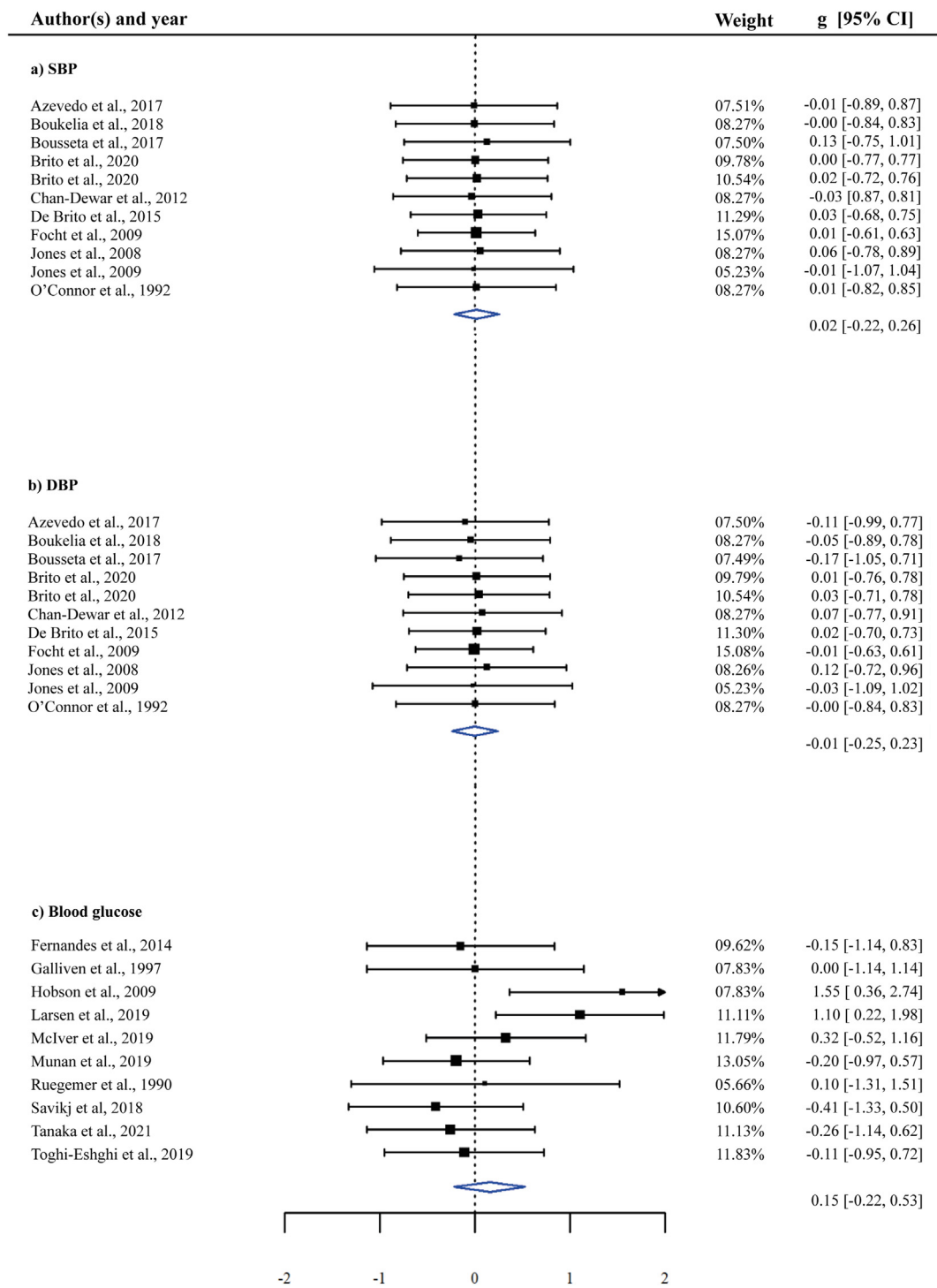


Fig. 2. Forest plot of the standardized effect sizes (hedges' g) for a) systolic blood pressure (SBP), b) diastolic blood pressure (DBP) and c) blood glucose. A negative value means the effect of exercise performed in the evening is greater than the effect of exercise performed in the morning. CI = confident interval.

3.4. Analysis of potential moderator variables

The moderation from sex, BMI, age, health status, exercise intensity, and duration did not reach statistical significance for any outcome when comparing morning vs. evening effects (all $P > 0.05$).

From the separate meta-analyses of morning and evening exercise we found that none of the outcomes were affected by the hour within the morning or within the evening in which exercise was performed ($P \geq 0.05$). For blood glucose in the morning, we observed that the

exercise-induced increase was not significant in healthy participants ($g = 0.27$) but significant in non-healthy participants (i.e., type 1 and type 2 diabetes, and mild sleep apnoea) ($g = 0.74$).

3.5. Risk of bias and quality assessment

The methodological quality of all trials included in the meta-analysis was assessed considering specific biases to cross-over design based on Cochrane's risk of bias tool.²⁰ According to these criteria, 47.5% of the

Table 2

Acute change in SBP, DBP and blood glucose after morning, evening, and morning vs. evening exercise.

	Morning MD	Evening MD	Morning vs. Evening MD
SBP	mmHg −5.54 [−8.58, −2.49]	mmHg −6.43 [−9.29, −3.56]	mmHg 1.43 [−1.47, 4.34]
DBP	−1.17 [−3.10, 0.76]	−0.92 [−2.16, 0.32]	0.02 [−1.37, 1.42]
Blood glucose	mmol/L 0.43 [0.09, 0.77]	mmol/L 0.04 [−0.12, 0.19]	mmol/L 0.32 [−0.11, 0.76]

Legend: SBP: systolic blood pressure; DBP: diastolic blood pressure; MD: mean difference. A negative value in morning vs. evening MD means favoring evening.

total items were categorized as having a low, 44.9% unclear, and 7.6% high risk of bias. Details of this quality assessment can be found in Table S4. The analyses of this variable as a potential moderator of effect sizes revealed non-significant results ($P > 0.05$ for all groups and outcomes), so the methodological quality of studies did not affect effect sizes on cardiovascular risk factors.

3.6. Sensitivity analysis

Only 1 study was influencing exercise effect on SBP in the morning,⁴¹ 1 study was influencing exercise effect on MBP in the morning and evening³⁹ and 1 study was influencing exercise effect on blood glucose in the evening and morning vs. evening.⁴⁴ Yet, the reductions of pooled effects after excluding them from analyses were not significant ($\Delta g = \leq 0.14$), so we decided to include them in the total effect size calculation. Lastly, we found no risk of publication bias (fail-safe N index range from 0 to 100 Egger's test: $P > 0.05$).

4. Discussion

We systematically reviewed and meta-analyzed the results of 22 studies aiming to better understand whether the acute effect of exercise on cardiovascular disease risk factors in adults differs when it is performed in the morning vs. the evening. Overall, we found no influence of the time of the day (i.e., morning vs. evening) on the effect of a single bout of exercise on blood pressure neither on blood glucose.

The results of this systematic review and meta-analysis should however be taken with caution. Although a total of 22 studies have been included, we present 4 different meta-analyses each one corresponding to a different outcome: SBP (11 studies)^{11–13,34–38,41,47}, DBP (11 studies)^{11–13,34–38,41,47}, MBP (7 studies)^{11–13,33,37,39} and blood glucose (10 studies).^{10,40,42–46,48,49,51} Further, qualitative differences between studies do exist (e.g., exercise protocols, health and training status, or sex). It should be noted as a limitation that the lack of statistical heterogeneity in any of the meta-analyses performed may be explained by the small sample size of included studies.

Exercise protocols consisted of aerobic training in most of the studies except for two of them, which used strength training,^{41,49} and a single study that used a mixed strength and aerobic training protocol.³⁴ Importantly, exercise intensity and duration differ between them. Also, some protocols were performed under hot and humid conditions.^{35,43} We considered data measured between 15 to 60 min post-exercise, which is a relatively wide range in which results may differ. Likewise, not all exercise protocols were performed at the same hour but within a wide range of hours differing in each study (i.e., 6:00 to 9:30 a.m. for morning exercise and 3:00 to 9:00 pm for evening exercise). Blood glucose and blood pressure present diurnal rhythmicity themselves^{53–55} and therefore their response to exercise may be different even within the same time slot. Of the 22 studies, only 6 included female

participants.^{34,38,42,46,48,49} We found few studies including trained participants^{35,36,38,40} while most studies included sedentary or recreationally active people. About half of the studies included participants with normal-weight^{12,33,47,35,36,38–43}, the rest included participants with overweight and obesity.^{11,13,34,37,44–46,49,56} Participants also differed in age, being the youngest sample of 21 years average³⁵ and the oldest of 65 years average.⁴⁶ A minor part of the total sample was composed of patients with pre-hypertension,¹³ hypertension,^{34,37} mild-sleep apnoea,⁴⁴ type I diabetes,^{48,49} and type II diabetes,^{10,46} being the rest healthy participants. However, when analyzing the moderator effects of exercise intensity and duration, hour within the morning and evening, sex, BMI, age, and health status we found no influence of any of the variables regarding the effect of morning vs. evening exercise. The lack of significant moderator effects may be due to the reduced number of studies included in each moderator level and, in the case of sex, to the reduced number of women participating in the studies.

The results of this meta-analysis indicate that morning and evening exercise produces similar acute hypotensive effects. This is in line with most of the studies^{33–36,38,39,41,47}. Discrepancies with other studies can be explained by health status (pre-hypertension),¹³ medication,³⁷ or inappropriate analysis (not taking into account baseline circadian rhythmicity).^{11,12} Albalak et al.⁸ found an association between morning physical activity and lower risk of CVD in general population. Interestingly, their results were mostly driven by women (58%), which is a lacking population in our meta-analysis. Differences in the studies' design need also to be considered. In epidemiological studies^{7–9} participants are organized into clusters according to the time of the day they are physically active, which is probably related to their individual circadian rhythmicity (i.e., chronotype). In contrast, in crossover studies each participant's chronotype may influence the response to morning and evening exercise. Sex and chronotype seem to be important when studying the effect of the time of the day of exercise.

In the present study, we did not find significant differences when comparing the acute effect of morning vs. evening exercise on blood glucose. However, the increase in blood glucose tended to be bigger after morning exercise. The rhythmicity of skeletal muscle's clock genes may explain these responses. Glucose uptake of the skeletal muscle cell dependent on the glucose transporter 4 is regulated by clock genes (specifically *CLOCK* and *ARNTL* genes⁵⁷). Interestingly, in animal models, *CLOCK* has been described to peak during the light phase in retina cells and to peak later, during the dark phase, in the skeletal muscle.⁵⁸ Therefore, glucose uptake by the skeletal muscle cells (and consequently clearance of blood glucose) may be enhanced in the dark phase (i.e., in the evening hours). Although health status did not moderate the morning vs. evening response of blood glucose, in the separate meta-analyses of morning exercise we observed a significant increase in non-healthy participants (most with diabetes mellitus) but not in healthy. We speculate cortisol and insulin circadian rhythmicity are involved in the mentioned dissimilarity. Free cortisol and insulin levels are higher in the morning.^{40,59} Cortisol is expected to produce an elevation in plasma glucose that results not notorious in healthy (because of the counteractive effect of insulin), but notorious in patients with type I or type II diabetes where insulin function is altered. Only studies that included participants with diabetes mellitus reported significant time-of-day differences in blood glucose response to exercise: an increase after morning but not after evening exercise,^{10,48,49} except for Munan et al.⁴⁶ in which patients presented well-managed diabetes and were taking lowering-glucose medication (not an accurate representation of the average population with diabetes). Thus, it may well be that exercising in the morning should be avoided by patients with diabetes mellitus.

4.1. Future perspectives

There is no available evidence to clarify whether health status, age, BMI, type of exercise, and hour within the morning and evening

influence the response to exercise at different times of the day. Similarly, we still need to elucidate whether this response is dependent on sex since studies including women are scarce. We neither found enough studies investigating blood lipids. Additionally, it would be of interest to investigate the acute response of other cardiovascular risks factors such as insulin or inflammatory markers.

We suggest some points to consider for future research. First, the resting diurnal rhythmicity present in blood pressure and blood glucose needs to be considered. Some studies highlight the importance of accounting for differences in initial values across conditions and the repeated measure design.^{38,47} For example, when data from the studies that reported diurnal differences in the hypotensive acute effect of exercise^{11–13,37} were analyzed in this meta-analysis, we found very small effect sizes when comparing morning and evening exercise effects. We recommend controlling for chronotype, as performed in a few of the included studies.^{13,37,40,41,45,47} It may also be interesting to control for peripheral temperature since changes in this factor can be attributed to alterations in circadian clocks.⁶⁰

5. Conclusion

The present preliminary findings reveal that exercise produces an acute reduction of systolic blood pressure independently of the time of the day at which it is performed. Similarly, exercise produces an acute increase in blood glucose independently of the time of the day. With the available literature, we could not make robust conclusions about the acute effect of the time of the day of exercise on cardiovascular disease risk factors. Further research is required to establish whether there is a diurnal variation of exercise on cardiovascular health and how it is related to health status, sex, or the type of exercise.

Registration

This systematic review and meta-analysis protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42021283350).

Confirmation of Ethical Compliance

The results presented in this work have not been published previously. This work is not under consideration for publication elsewhere. The publication of this work is approved by all authors and by the responsible authorities where the work was carried out.

Declaration of Interest Statement

Authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jsams.2023.03.004>.

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