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Chronotype-aligned exercise timing in middle-aged adults at cardiometabolic risk: a randomised controlled trial

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ABSTRACT

Objective To investigate whether aligning exercise timing with chronotype enhances cardiometabolic and sleep-related benefits in sedentary adults with cardiovascular risk factors.

Methods In this 12-week randomised controlled trial conducted in Lahore, Pakistan (January–June 2025), 150 sedentary adults (aged 40–60) with at least one cardiovascular risk factor were recruited and categorised as morning-type or evening-type using the Morningness-Eveningness Questionnaire and validated by 48 hour core body temperature monitoring. Participants were randomised into a chronotype-aligned exercise (CAE) group exercising at their preferred time, or a chronotype-misaligned exercise (CME) group exercising at their non-preferred time. Moderate-intensity aerobic training (5 sessions/week, 40 min/session) was supervised. Primary outcomes included systolic and diastolic blood pressure (BP) and heart rate variability (RMSSD); secondary outcomes included peak oxygen consumption (VO_2 peak), low density lipoprotein (LDL), fasting glucose and sleep quality (PSQI), assessed pre- and post-intervention.

Results Of 150 randomised participants, 134 completed the study (CAE: n=64; CME: n=70). CAE led to significantly greater improvements in systolic BP (−10.8 vs −5.5 mm Hg, p=0.002), diastolic BP, RMSSD, VO_2 peak, LDL, fasting glucose and PSQI scores compared with CME. Repeated measures analysis of variance (ANOVA) revealed significant group×time interactions across all outcomes (eg, systolic BP: η^2=0.095, p=0.005). The reduction in systolic BP in the CAE group was substantial and significantly greater than in the CME group.

Conclusion Aligning exercise timing with individual chronotype significantly enhances cardiometabolic and sleep-related outcomes in at-risk adults. Chronotype-based exercise prescriptions may offer a cost-effective, personalised approach to improving cardiovascular health.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exercise reduces cardiometabolic risk, but its benefits may depend on the timing of activity relative to an individual's circadian rhythm. Chronotype (morningness or eveningness preference) influences exercise performance and adherence.

WHAT THIS STUDY ADDS

⇒ This randomised controlled trial shows that aligning exercise timing with chronotype enhances cardiometabolic outcomes in middle-aged adults at risk. Early chronotypes benefited more from morning exercise, while late chronotypes showed better results with evening sessions. Chronotype-aligned exercise also improved adherence and metabolic markers compared with mismatched timing.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support the inclusion of chronotype assessment in exercise prescriptions for cardiometabolic prevention. Personalised, time-matched exercise interventions may become a practical strategy in clinical and public health settings, potentially leading to better outcomes and improved engagement. Future research and guidelines may consider circadian factors as a core component of lifestyle-based disease prevention.

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality globally, responsible for approximately 18 million deaths each year.[1] While preventive strategies such as increased physical activity, weight control and improved sleep hygiene have been widely promoted, the growing burden of non-communicable diseases suggests that current population-level interventions may lack necessary personalisation. One emerging area of interest in preventive medicine is the role of circadian biology, specifically chronotype, in modulating individual responses to lifestyle interventions like exercise.

Chronotype refers to an individual's biological predisposition toward morningness or eveningness, affecting sleep–wake patterns, hormonal secretion and energy availability across the day.[2] This internal timing mechanism is regulated by the circadian clock, a complex system governed by the suprachiasmatic nucleus and peripheral oscillators, which in turn influence various physiological processes including blood pressure, heart rate, glucose metabolism and vascular function.[3] As such, individuals differ not only

in their preferred sleep and wake times but also in the timing of optimal physical performance and cardiovascular responsiveness to exercise.[4]

Despite the well-established cardiovascular benefits of regular aerobic exercise, including improved endothelial function, reduced blood pressure, better lipid profiles and increased peak oxygen consumption (VO_2 peak), previous research suggests that exercise efficacy is modulated by time-of-day and individual circadian rhythms.[5] Morning-type individuals often show improved performance and mood responses when exercising earlier in the day, while evening types typically demonstrate better cardiovascular and muscular function during late-day exercise sessions.[6] These findings imply that a 'one-size-fits-all' approach to exercise timing may fail to account for biological variability that could influence both adherence and outcomes.

Furthermore, a mismatch between biological and social schedules, often termed social jetlag, has been linked to increased cardiovascular risk, including hypertension, poor glycaemic control and systemic inflammation.[7] Social jetlag is especially prevalent among evening-types forced into morning routines, potentially diminishing the effectiveness of early-day exercise interventions in these individuals. When exercise is prescribed at times misaligned with chronotype, adherence may suffer, and physiological adaptations may be blunted.[8]

Recent experimental studies have provided preliminary support for the benefits of personalised exercise timing. For instance, hypertensive adults who exercised in alignment with their chronotype experienced significantly greater reductions in blood pressure and improvements in heart rate variability (HRV) compared with those who exercised at non-preferred times.[9] Similarly, another study found that chronotype-aligned training led to enhanced sleep quality and greater improvements in cardiorespiratory fitness than conventional exercise schedules.[10] These findings suggest that synchronising exercise with an individual's biological rhythm may optimise cardiovascular outcomes, improve intervention adherence and offer a more targeted preventive strategy. Building on this evidence, the present study investigates whether aligning exercise timing with chronotype improves cardiovascular health in at-risk adults by assessing key indicators such as blood pressure, heart rate variability, VO_2 peak, lipid profiles and sleep quality.

PATIENTS AND METHODS

Participant recruitment and eligibility

This randomised controlled trial was conducted between January and June 2025 in Lahore, Pakistan. It was registered with the ISRCTN registry (ISRCTN14276441). Participants were recruited from the outpatient departments of internal medicine and cardiology at seven different government hospitals of Lahore. Additional outreach was conducted via hospitals' noticeboards, affiliated clinics, community health initiatives and digital media platforms. Eligible individuals were adults between 40 and 60 years of age. This age range was chosen because it represents a critical midlife period during which cardiovascular risk factors often emerge and stabilise, while circadian rhythms remain relatively intact.[11] It also avoids the circadian variability commonly seen in younger adults and the complex medication and comorbidity profiles associated with older populations.[12]

Sample size estimation was conducted using G*Power for a repeated measures analysis of variance (ANOVA) assessing the interaction between group (chronotype-aligned vs chronotype-misaligned) and time (pre- and post-intervention). Assuming a small-to-medium effect size (f=0.15). The effect size was estimated based on previous studies investigating time-of-day variations in exercise outcomes on cardiovascular and metabolic parameters.[13] With an α level of 0.05, a power of 0.80, two groups, and two measurement time points with an assumed correlation of 0.5 between repeated measures, the required total sample size was calculated to be 148. To account for potential dropouts and ensure sufficient power, a total of 150 participants were recruited.

A total of 183 participants were initially screened for eligibility. Of these, 150 participants met the inclusion criteria and were enrolled in the study. The remaining 33 participants were excluded for the following reasons: not meeting age or body mass index (BMI) criteria (n=10), absence of cardiovascular risk factors or sedentary lifestyle (n=8), irregular sleep schedules or diagnosed sleep disorders (n=5), current use of excluded medications (n=6), and incomplete baseline assessments or inability to commit to the intervention schedule (n=4).

Participants were included if they had at least one cardiovascular risk factor, such as prehypertension or stage 1 hypertension (defined by systolic blood pressure (SBP) 120–139 mm Hg or diastolic blood pressure (DBP) 80–89 mm Hg, measured using an automated sphygmomanometer after 10 min of seated rest), overweight or obesity (BMI ≥25 kg/m² based on measured height and weight), and a sedentary lifestyle (no structured physical activity ≥1 session/week in the past 3 months), confirmed via the Global Physical Activity Questionnaire.[14] This standardised instrument evaluates physical activity across three domains: work, transport and recreational activities, as well as sedentary behaviour. Participants were included if they had impaired fasting glucose (IFG), defined as fasting plasma glucose between 100–125 mg/dL (5.6–6.9 mmol/L), based on American Diabetes Association 2024 criteria. IFG indicates pre-diabetes and is associated with increased cardiovascular risk and progression to type 2 diabetes.[15]

A family history of premature CVD was also an inclusion criterion, defined as CVD in a first-degree male relative before age 55 years or a female relative before age 65. Family history is a strong non-modifiable risk factor for CVD, reflecting genetic and shared environmental influences.[16]

Individuals were excluded if they had clinically diagnosed cardiovascular or metabolic diseases such as coronary artery disease or diabetes. These conditions were confirmed through medical records, physician diagnosis or laboratory results (eg, previous history of myocardial infarction, angiographic evidence of coronary artery disease or HbA1c (Glycated haemoglobin) ≥6.5% or fasting glucose ≥126 mg/dL for diabetes). Participants were also excluded if they worked night shifts, had irregular sleep schedules or had diagnosed sleep disorders such as insomnia or obstructive sleep apnoea assessed through clinical history and, when relevant, previous sleep study reports.

Furthermore, those taking medications known to influence significantly cardiovascular or circadian regulation, such as β-blockers, calcium channel blockers, sedatives or recently initiated statins or glucose-lowering drugs, were excluded. However, participants on stable doses of antihypertensives, statins or oral hypoglycaemics for at least 6 months before the study were eligible, and all medication use was documented at baseline and monitored throughout the intervention period.

Chronotype assessment and group allocation

Chronotype was assessed at baseline using the Morningness-Eveningness Questionnaire (MEQ), a validated instrument that classifies individuals based on their circadian preferences.[17] Participants scoring 59 or higher were categorised as morning-types, while those scoring 41 or below were classified as evening-types. Individuals with intermediate scores between 42 and 58 were excluded to ensure a clear separation of chronotypes to complement subjective chronotype assessment. Core body temperature was measured as an objective physiological marker of circadian rhythm. Continuous temperature monitoring was conducted over 48 hours before the intervention using DataLoggers with skin sensors (iButton DS1922L),[10] a validated skin-worn device that estimates core temperature via heat flux technology.[18] Temperature rhythm profiles were used to confirm circadian phase alignment and validate MEQ-based chronotype classification, ensuring accurate timing of exercise relative to the biological clock.[19] This additional measure helped validate the timing of exercise interventions relative to the biological clock.

After chronotype classification, participants were randomised using computer-generated permuted blocks of size 4 and 6, stratified by chronotype (morning, evening) and cardiovascular risk level (low, moderate). Block sizes were randomly varied to maintain allocation concealment, stratified by chronotype and cardiovascular risk level. Participants in the chronotype-aligned exercise (CAE) group performed exercise sessions at their preferred circadian time, morning-types in the morning and evening-types in the evening. In contrast, participants in the chronotype-misaligned exercise (CME) group exercised at their non-preferred time, morning-types in the evening and evening-types in the morning.

Exercise intervention protocol

Exercise sessions were scheduled from 8:00 to 11:00 am for morning sessions and 6:00 to 9:00 pm for evening sessions in the University of Lahore teaching hospital. These time windows were selected based on both circadian rhythm physiology and practical feasibility. Morning exercise was aligned with the post-awakening rise in core body temperature and cortisol levels, which typically enhance alertness, cardiovascular response and muscular efficiency during the first few hours after waking.[20] Evening sessions coincided with the circadian peak in body temperature and muscle function, typically occurring in the early evening, which is associated with improved exercise performance and lower perceived exertion.[21] Additionally, these time windows allowed flexibility for participants to attend supervised sessions before or after work hours, supporting adherence and real-world applicability.

The exercise intervention followed guidelines established by the American College of Sports Medicine[22] and spanned a total of 12 weeks, a duration commonly used in clinical exercise trials to elicit meaningful improvements in cardiovascular health, blood pressure regulation and autonomic function. Twelve weeks of structured aerobic training is sufficient to produce significant changes in blood pressure, HRV and metabolic outcomes among individuals with cardiovascular risk factors.[23] This timeframe also balances physiological effectiveness with participant adherence and feasibility in real-world settings. The intervention involved moderate-intensity aerobic training using brisk walking or treadmill walking, depending on participant preference. Each session lasted 40 min and included a 5 min warm-up, a 30 min main aerobic phase targeting 60–70% of age-predicted maximum heart rate, and a 5 min cool-down. This duration has been shown to reduce blood pressure and enhance autonomic function effectively.[24] Participants were instructed to perform five sessions per week, and all sessions were supervised onsite at the hospital gym. To monitor and maintain target heart rate zones during exercise, Polar H10 heart rate sensors were used, offering real-time heart rate tracking via Bluetooth connection to physiotherapist-operated tablets.

A physician was present during all supervised sessions to address any adverse events. Participants were instructed to stop exercising immediately if they experienced chest discomfort, dizziness, fainting, palpitations, nausea or extreme fatigue. Adherence to the intervention was monitored through session attendance logs and weekly self-reports.

Participants were instructed to attend at least 90% of the prescribed sessions over the 12-week period. Adherence ≥90% was considered acceptable and was used as a benchmark for inclusion in per-protocol analyses.

Outcome measures

The primary outcome measures SBP, DBP and HRV were assessed at baseline (week 0), and within 3 days following the completion of the intervention (week 12).

Blood pressure was measured using a validated automated sphygmomanometer (Omron HEM-907), following international guidelines.[25] Measurements were taken after 24 hours of the last exercise session to avoid acute post-exercise effects and were taken in a quiet room after 10 min of seated rest. Three readings were obtained, and the average of the last two was used.

HRV was assessed at week 12 (day 3 post-intervention), during morning hours (8:00 to 10:00 am) to minimise circadian variation.[26] Participants rested supine for 10 min before a 5 min ECG was recorded using the Biopac MP36 system. HRV parameters were analysed with Kubios HRV software, following standardised measurement protocols.[27]

Secondary outcomes were assessed at baseline and after 12 weeks of intervention (preferably day 3 or 4 after intervention), depending on participant availability.

Estimated VO_2 peak was assessed using the Bruce submaximal treadmill protocol on day 4 post-intervention, ensuring 48 hours of recovery from the final exercise session. Heart rate was continuously monitored using Polar H10 sensors, and testing ceased at 85% of age-predicted maximum heart rate. Direct measurement of maximal oxygen uptake using a metabolic cart was not performed; therefore, values represent estimated peak aerobic capacity rather than true VO_2 max.[28]

Blood samples for lipid profile, fasting glucose and HbA1c were collected in the morning of day 3 or 4 following a 12 hour overnight fast, using standard enzymatic assays and immunoturbidimetric methods.[29]

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) on day 3, referring to the past month, allowing participants to reflect on sleep changes throughout the intervention.[30] Although the PSQI was administered on day 3 of the study, participants were instructed to reflect on their sleep habits over the month preceding the intervention, to ensure that baseline data accurately captured pre-intervention sleep quality.

Exercise adherence was monitored continuously throughout the intervention using supervised session attendance logs, weekly adherence interviews based on the Exercise Adherence Rating Scale.[31]

Exercise performance was additionally assessed using total treadmill exercise time (minutes) achieved during the Bruce submaximal protocol. The Bruce protocol consists of progressive 3 min stages of increasing speed and grade. Total treadmill time was calculated from the start of the test to the final completed stage, including partial stages if participants stopped before a full stage was completed.[32]

Blinding procedures

Full blinding was not feasible due to the nature of the exercise timing intervention and the involvement of the investigator in direct data collection. Outcome assessors were therefore not blinded. However, to minimise measurement and expectation bias, several strategies were implemented. Participants were not informed of the specific study hypothesis or of their group classification as 'aligned' or 'misaligned', reducing the risk of expectancy effects.

Standardised protocols and automated devices were used for all primary and secondary outcome measurements to reduce assessor bias.

Statistical analysis

All analyses were performed using standard statistical software Statistical Package for the Social Sciences (SPSS) version 26.0. Continuous variables are presented as mean±standard deviation (SD), and categorical variables as counts and percentages. Normality of continuous outcome variables was assessed using the Shapiro-Wilk test and confirmed by visual inspection of histograms and Q–Q plots. All primary and secondary outcomes demonstrated approximately normal distributions.

Baseline characteristics between the CAE and CME groups were compared descriptively to assess group balance. Independent-samples t tests were used for continuous variables and χ^2 tests for categorical variables, as appropriate.

Primary analyses examining the effects of exercise timing on cardiovascular, metabolic, fitness, autonomic and sleep outcomes were conducted using repeated measures ANOVA, with group (CAE vs CME) as the between-subject factor and time (baseline vs week 12) as the within-subject factor. Group×time interaction effects were used to determine differential responses between intervention groups. Effect sizes were reported as partial eta squared (η^2), and Cohen's f was calculated to quantify the magnitude of interaction effects.

Within-group changes from baseline to week 12 were assessed using paired-samples t tests. Between-group differences in change scores were calculated, and effect sizes were expressed as Cohen's d. Relative percentage changes were calculated for body weight and BMI outcomes.

Prespecified subgroup analyses were performed to explore differential changes in SBP by sex, baseline hypertension status and chronotype using stratified repeated measures models. Interaction p values were reported to assess consistency of intervention effects across subgroups.

Exploratory descriptive analyses comparing morning-type and evening-type participants are presented in online supplemental table 1. These analyses were intended to provide contextual insights into chronotype-related patterns of response and were not subjected to formal hypothesis testing.

Multiple linear regression analysis was conducted to identify independent predictors of change in SBP at 12 weeks (online supplemental table 2). The model included intervention group, baseline SBP, age, sex, chronotype and medication use. Model fit was assessed using R^2, and regression coefficients (B) with corresponding p values were reported.

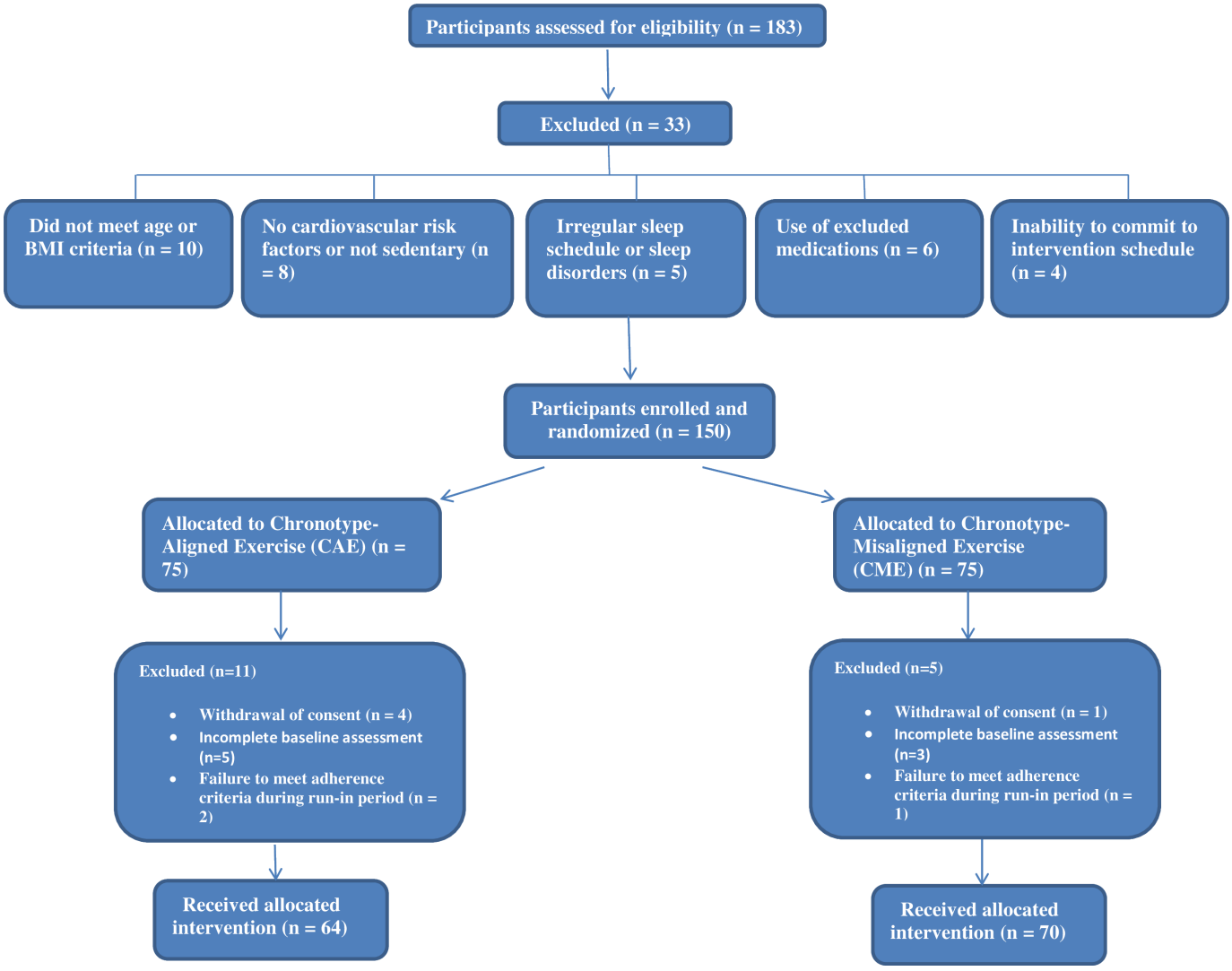

Figure 1 Flow diagram of participant recruitment and screening. BMI, body mass index.

All tests were two-sided, and statistical significance was defined as $p<0.05$. The central graphical summary (see later) was created using BioRender.

RESULTS

The flow diagram in figure 1 outlines the recruitment, screening, randomisation, intervention allocation, follow-up and final analysis of participants in this randomised controlled trial examining CAE versus CME. A total of 183 individuals were screened for eligibility, of whom 33 were excluded due to not meeting inclusion criteria, irregular sleep schedules, medication use or incomplete baseline assessments. Participants in the CAE group performed supervised moderate-intensity aerobic exercise at their preferred circadian time (morning for morning-types and evening for evening-types), while those in the CME group exercised at their non-preferred time. During follow-up, additional exclusions occurred due to withdrawal of consent, inadequate adherence or incomplete data, resulting in a final analytic sample of 134 participants. The figure illustrates participant retention, reasons for exclusion and the number of participants included in the primary and secondary outcome analyses at 12 weeks.

Table 1 presents the baseline characteristics of the study population (n=134) stratified by CAE (n=64) and CME (n=70) groups. The overall sample included 78 males (58.2%) and 56 females (41.8%), with a mean age of 48.6±8.1 years and a mean BMI of 28.7±3.4 kg/m². The prevalence of hypertension and prehypertension was 32.8% and 46.3%, respectively, while 83.6% of participants were classified as overweight or obese (BMI ≥25 kg/m²). All participants reported a sedentary lifestyle. A family history of cardiovascular disease was present in 43.3% of the cohort. Regarding chronotype, 52.2% were classified as morning-types and 47.8% as evening-types. Medication use included antihypertensive therapy (21.6%), statins (13.4%), diabetes medications such as metformin (16.4%), and other stable medications (23.9%). Baseline characteristics were similar between the CAE and CME groups, with no substantial differences observed in sex distribution, age, BMI, blood pressure categories, chronotype or medication use.

Table 1 Baseline characteristics

Characteristic	Total (N=134)	CAE (n=64)	CME (n=70)
Sex			
Male, n (%)	78 (58.2%)	39 (60.9%)	39 (55.7%)
Female, n (%)	56 (41.8%)	25 (39.1%)	31 (44.3%)
Age (years), mean±SD	48.6±8.1	48.3±8.3	48.9±7.9
BMI (kg/m²), mean±SD	28.7±3.4	28.6±3.3	28.9±3.5
Hypertension, n (%)	44 (32.8%)	21 (32.8%)	23 (32.9%)
Pre-hypertension, n (%)	62 (46.3%)	30 (46.9%)	32 (45.7%)
Overweight/obese (BMI ≥25)	112 (83.6%)	53 (82.8%)	59 (84.3%)
Sedentary lifestyle, n (%)	134 (100%)	64 (100%)	70 (100%)
Family history of CVD, n (%)	58 (43.3%)	27 (42.2%)	31 (44.3%)
Chronotype (MEQ)			
Morning type, n (%)	70 (52.2%)	34 (53.1%)	36 (51.4%)
Evening type, n (%)	64 (47.8%)	30 (46.9%)	34 (48.6%)
Medication use			
Antihypertensive medication, n (%)	29 (21.6%)	14 (21.9%)	15 (21.4%)
Statin use, n (%)	18 (13.4%)	8 (12.5%)	10 (14.3%)
Diabetes medication (eg, metformin), n (%)	22 (16.4%)	10 (15.6%)	12 (17.1%)
Other stable medications, n (%)	32 (23.9%)	16 (25.0%)	16 (22.9%)

Normality of continuous outcome variables (systolic and diastolic blood pressure, RMSSD, VO_2 peak, LDL, glucose, and PSQI score) was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q–Q plots.
BMI, body mass index; CVD, cardiovascular disease; LDL, low density lipoprotein; MEQ, Morningness-Eveningness Questionnaire ; PSQI, Pittsburgh Sleep Quality Index; RMSSD, root mean square of successive differences; a time-domain measure of heart rate variability; VO_2 peak, peak oxygen consumption.

All variables demonstrated approximately normal distributions ($p>0.05$), with visual plots showing no major deviations from normality.

Table 2 shows the results of repeated measures ANOVA examining group×time interaction effects for cardiovascular, metabolic, exercise performance and sleep outcomes following the 12-week intervention (Table 2).

Repeated measures ANOVA demonstrated significant group×time interactions for all assessed outcomes, indicating differential pre- to post-intervention changes between the CAE and CME groups. Significant interaction effects were observed for SBP ($F(1,132)=13.9$, $p=0.005$, $\eta^2=0.095$), DBP ($F(1,132)=9.2$, $p=0.003$, $\eta^2=0.065$), and HRV (RMSSD) ($F(1,132)=11.4$, $p=0.001$, $\eta^2=0.079$), reflecting greater improvements in autonomic and blood pressure regulation in the CAE group.

Exercise capacity and performance outcomes also showed significant interactions, including estimated VO_2 peak ($F(1,132)=7.1$, $p=0.009$, $\eta^2=0.051$), total treadmill exercise time ($F(1,132)=8.2$, $p=0.006$, $\eta^2=0.058$), and Bruce protocol stage achieved ($F(1,132)=7.8$, $p=0.008$, $\eta^2=0.053$), indicating superior aerobic and functional performance adaptations with chronotype-aligned exercise timing.

Significant group×time effects were further observed for LDL cholesterol ($F(1,132)=6.8$, $p=0.010$, $\eta^2=0.049$), fasting glucose ($F(1,132)=4.9$, $p=0.028$, $\eta^2=0.036$), and sleep quality (PSQI) ($F(1,132)=15.5$, $p<0.001$, $\eta^2=0.105$). Effect sizes ranged from small to moderate, with the largest effects observed for sleep quality and SBP. Partial eta squared (η^2) represents the proportion of variance attributable to the group×time interaction.

Table 3 shows within-group changes from baseline to week 12 in the CAE and CME groups. The CAE group had larger improvements across all outcomes. SBP decreased by 10.8 mm Hg (135.0±9.5 to 124.2±8.2, p=0.002) versus 5.5 mm Hg in CME (134.6±9.1 to 129.1±8.9, p=0.031), and DBP decreased by 7.3 mm Hg versus 3.3 mm Hg. RMSSD increased by 12.7 ms in CAE compared with 5.8 ms in CME. Estimated VO_2 peak rose by 4.4 mL/kg/min in CAE versus 2.3 mL/kg/min in CME, while total treadmill time increased by 4.3 min versus 1.5 min, and Bruce protocol stage improved by 1.1 versus 0.5 stages. LDL decreased by 13.7 mg/dL versus 7.6 mg/dL, fasting glucose by 6.6 mg/dL versus 3.2 mg/dL, and PSQI scores improved by 3.4 versus 1.2 points. These results indicate that chronotype-aligned exercise produces greater improvements in blood pressure, autonomic function, aerobic capacity, metabolic markers and sleep quality compared with misaligned exercise.

To determine whether certain subgroups benefited more from aligned exercise, a stratified analysis of SBP change was performed (table 4). Both males and females

Table 2 Effects of chronotype-aligned versus misaligned exercise on cardiovascular and metabolic outcomes (group×time interaction, repeated measures ANOVA)

Outcome	F(1,132)	P value	η^2	Cohen's f
Systolic BP	13.9	0.005	0.095	0.324
Diastolic BP	9.2	0.003	0.065	0.263
RMSSD (HRV)	11.4	0.001	0.079	0.294
VO_2 peak	7.1	0.009	0.051	0.231
Total treadmill time (min)	8.2	0.006	0.058	0.241
Bruce protocol stage	7.8	0.008	0.053	0.230
LDL	6.8	0.010	0.049	0.226
Fasting glucose	4.9	0.028	0.036	0.193
PSQI (sleep quality)	15.5	< 0.001	0.105	0.341

Values represent results from repeated measures ANOVA examining the group×time interaction between chronotype-aligned exercise (CAE) and chronotype-misaligned exercise (CME) groups across baseline and week 12. F values are reported with df (*1,132*). η^2 indicates partial eta squared, representing the proportion of variance explained by the group×time interaction. Cohen's f represents effect size for repeated measures ANOVA and was derived from partial eta squared. VO_2 peak values were estimated using the Bruce submaximal treadmill protocol and were not directly measured with a metabolic cart. Total treadmill time (min) refers to the total duration completed during the Bruce submaximal treadmill test, including partial stages. Bruce protocol stage reflects the highest fully completed stage achieved during the submaximal treadmill test. PSQI, Pittsburgh Sleep Quality Index; higher scores indicate poorer sleep quality. RMSSD, root mean square of successive differences; a time-domain measure of heart rate variability (HRV). Statistical significance was defined as $p<0.05$.
ANOVA, analysis of variance; BP, blood pressure; LDL, low density lipoprotein; VO_2 peak, peak oxygen consumption.

in the CAE group showed nearly double the improvement in BP reduction compared with their CME counterparts. Participants with hypertension at baseline experienced the largest benefit, with a mean reduction of 13.6 mm Hg in the CAE group versus 7.1 mm Hg in the CME group ($p<0.001$). Similarly, both morning and evening chronotypes in the CAE group showed significantly greater reductions than in the CME group ($p\leq0.004$). These findings highlight the potential clinical value of chronotype-aligned exercise in optimising blood pressure outcomes.

Online supplemental table 1 presents exploratory descriptive data comparing cardiovascular, autonomic, metabolic, fitness, body composition, and sleep-related outcomes between morning-type and evening-type participants at baseline and after 12 weeks of intervention. Morning-type participants and evening-type participants were classified based on chronotype assessment at study entry. Outcomes include blood pressure, HRV (RMSSD), estimated aerobic fitness parameters derived from a submaximal treadmill test, lipid and glucose measures, anthropometric indices and subjective sleep quality.

Across both chronotype groups, improvements were observed at week 12 in SBP, DBP, HRV, estimated VO_2 peak, treadmill performance, lipid profile, fasting glucose, body weight, BMI and sleep quality scores. While both morning- and evening-type participants demonstrated favourable changes over time, the magnitude of improvement appeared descriptively greater in morning-type participants for several cardiovascular, autonomic and fitness-related measures. These data are presented to provide speculative insights into chronotype-related patterns of response and were not intended for formal hypothesis testing.

A multiple linear regression analysis was conducted to identify predictors of change in SBP (Δ SBP) after 12 weeks in online supplemental table 2. The model was

Table 3 Within-group changes in cardiometabolic and sleep outcomes from baseline to week 12 in chronotype-aligned (CAE) and chronotype-misaligned (CME) exercise groups and effect sizes

Outcome	CAE baseline	CAE week 12	P value	CME baseline	CME week 12	P value	Δ between groups	Cohen's d
Systolic BP (mmHg)	135.0±9.5	124.2±8.2	0.002	134.6±9.1	129.1±8.9	0.031	−5.3 mmHg	1.00
Diastolic BP (mmHg)	86.1±6.6	78.8±6.1	0.005	85.7±6.8	82.4±6.3	0.014	−4.0 mmHg	0.70
RMSSD (ms)	29.1±9.0	41.8±10.1	0.004	28.5±9.2	34.3±9.5	0.033	+6.9 ms	0.80
VO_2 peak (mL/kg/min)	27.1±4.3	31.5±4.6	0.003	27.3±4.1	29.6±4.3	0.021	+2.1	0.55
Total treadmill time (min)	12.5±2.1	16.8±2.3	0.002	12.6±2.0	14.1±2.2	0.018	+2.7 min	0.60
Bruce protocol stage	3.2±0.6	4.3±0.7	0.001	3.2±0.5	3.7±0.6	0.022	+0.6 stage	0.58
LDL (mg/dL)	132.9±21.0	119.2±17.9	0.007	133.5±22.5	125.9±20.7	0.015	−6.7 mg/dL	0.40
Fasting glucose (mg/dL)	106.1±10.5	99.5±9.8	0.008	105.8±10.6	102.6±10.2	0.023	−3.1 mg/dL	0.35
Body weight (kg)	79.2±11.3	77.6±10.9	0.004	79.5±10.8	78.7±10.7	0.021	−0.8 kg (−1.0%)	0.45
BMI (kg/m²)	28.7±3.4	28.1±3.2	0.004	28.9±3.5	28.6±3.4	0.021	−0.3 (−1.0%)	0.40
PSQI score	8.3±2.1	4.9±1.7	0.006	8.2±2.2	7.0±1.8	0.030	−2.2 points	0.85

Δ between groups represents the difference in change scores from baseline to week 12. Relative change (%) is shown in parentheses for body weight and BMI. Values are mean±SD.
BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; PQSI, Pittsburgh Sleep Quality Index; RMSSD, root mean square of successive differences; a time-domain measure of heart rate variability; VO_2 peak, peak oxygen consumption.

Table 4 Subgroup analysis of changes in systolic blood pressure (Δ SBP) over 12 weeks by sex, hypertension status and chronotype in chronotype-aligned (CAE) and chronotype-misaligned (CME) groups

Subgroup	CAE (n)	Δ SBP (mean±SD)	CME (n)	Δ SBP (mean±SD)	Group×time p value
Sex					
Male	27	−10.1±4.2	28	−5.4±3.8	0.002
Female	37	−10.9±4.7	42	−5.2±3.9	0.001
Hypertension status					
Hypertensive at baseline	18	−13.6±4.8	20	−7.1±4.3	<0.001
Normotensive at baseline	46	−9.4±4.1	50	−4.6±3.7	0.003
Chronotype					
Morning type	35	−11.2±4.4	38	−5.8±4.0	0.001
Evening type	29	−9.9±4.3	32	−5.0±3.6	0.004

statistically significant (R^2=0.39, p=0.004), explaining 39% of the variance in SBP reduction.

CAE was the strongest independent predictor, associated with a significantly greater reduction in SBP compared with misaligned exercise (B=−5.18, p<0.001). Higher baseline SBP (B=−0.21, p=0.003) and being on antihypertensive medication (B=−2.91, p=0.009) were also significant predictors of greater blood pressure reduction. Age, sex and chronotype alone were not significant contributors. These findings underscore the importance of aligning exercise timing with chronotype and ensuring adherence for optimal blood pressure outcomes.

Figure 2 shows a central graphical summary of the randomised trial comparing CAE and CME exercise over 12 weeks. Aligning exercise timing with the biological clock resulted in synchronised circadian rhythms and greater improvements in SBP, aerobic capacity (VO_2 peak), HRV (RMSSD) and sleep quality compared with misaligned exercise. Blue indicates greater improvements in CAE, and orange indicates smaller improvements in CME.

DISCUSSION

Both the CAE and CME groups demonstrated significant improvements in cardiovascular risk factors, aerobic fitness and sleep quality over the 12-week intervention,

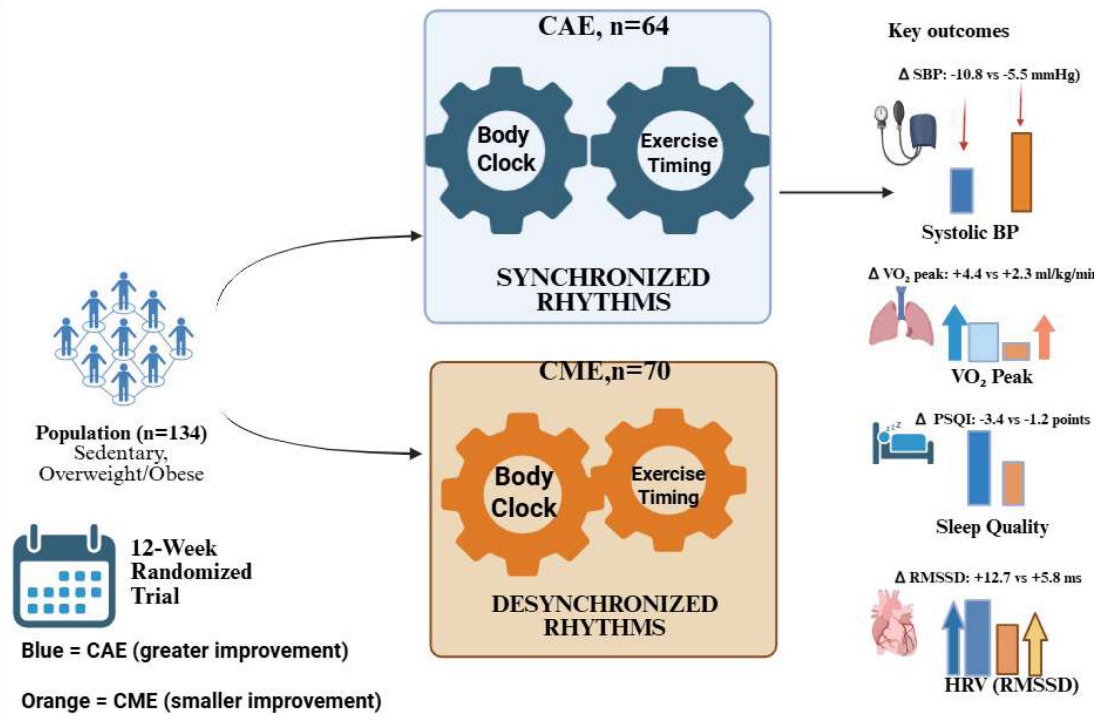

Figure 2 Graphical overview of chronotype-aligned (CAE) versus chronotype-misaligned (CME) exercise and associated outcomes. HRV (RMSSD), heart rate variability (root mean square of successive differences); PQSI, Pittsburgh Sleep Quality Index; SBP, systolic blood pressure; VO_2 peak, peak oxygen consumption.

confirming the well-established benefits of regular moderate-intensity aerobic exercise.

This study adds to a growing body of evidence suggesting that the timing of exercise when aligned with an individual's internal biological clock can significantly enhance health outcomes. Notably, the intervention effects were consistent across sex and chronotype categories and most pronounced among individuals with hypertension. This suggests that chronotype-aligned exercise may be broadly applicable but especially beneficial for those at highest cardiovascular risk. These results align with prior research indicating that circadian misalignment, such as through shift work, social jetlag or irregular activity schedules, is associated with elevated blood pressure and adverse cardiometabolic outcomes.[7] Chronotype-specific interventions may therefore represent a targeted strategy to mitigate these risks, particularly in populations already burdened by cardiovascular dysregulation.

The stronger effect in individuals with hypertension could be explained by heightened sensitivity to autonomic imbalance and circadian disruption in this group.[33] Chronotype-aligned exercise may help stabilise circadian rhythm-driven fluctuations in cortisol, melatonin and sympathetic tone, all of which are implicated in the pathogenesis of hypertension and cardiovascular disease.[34] Furthermore, prior studies have shown that hypertensive individuals exhibit exaggerated morning blood pressure surges and diminished nocturnal dipping, both of which are normalised to some extent with well-timed exercise.[35]

In addition, the regression analysis emphasised that chronotype-aligned exercise timing, alongside baseline systolic pressure, medication use and adherence, independently predicted the magnitude of blood pressure reduction. This underscores the importance of a multifactorial approach, integrating behavioural timing with clinical care. Notably, adherence itself was higher in the chronotype-aligned group, suggesting improved feasibility and acceptability when interventions are designed in accordance with individuals' innate biological patterns, a key insight for translational application.[36]

From a mechanistic perspective, these results are consistent with findings from animal and human models indicating that circadian misalignment impairs vascular function, glucose metabolism and autonomic regulation effects that are mitigated when activity is timed to match internal circadian phase.[20] Aligning exercise with chronotype may entrain peripheral clocks in skeletal muscle, adipose tissue and vasculature more effectively, enhancing metabolic efficiency and reducing inflammation, both critical factors in cardiometabolic health.[37]

These findings emphasise that the effectiveness of exercise extends beyond its frequency and duration to include timing. Integrating the principle of 'chrono-exercise' scheduling workouts according to an individual's internal biological clock may offer a novel and impactful approach to enhancing outcomes in preventive cardiovascular and metabolic health.

Limitations

This study was limited to government hospitals in Lahore with participants mostly from middle- or lower-income backgrounds, which may affect the generalisability of the findings to other regions or socioeconomic groups. The exclusion of individuals with intermediate chronotypes limits applicability to the broader population. Due to the visible nature of the intervention, full blinding was not possible, which may have introduced some performance or measurement bias. The 12-week duration was sufficient for short-term effects but does not provide insight into long-term outcomes or sustainability. Although only participants on stable medication regimens were included, drug effects may still have influenced results. In addition, VO_2 peak was estimated using a submaximal treadmill protocol rather than being directly measured with a metabolic cart, which may limit measurement precision.

CONCLUSION

This study demonstrates that regular aerobic exercise leads to significant improvements in cardiovascular risk factors and fitness in middle-aged adults with preclinical risk factors, regardless of exercise timing. However, aligning aerobic exercise with an individual's chronotype resulted in consistently greater reductions in blood pressure and larger improvements in HRV and fitness compared with CME. These findings highlight the added value of incorporating circadian biology into exercise prescription to optimise cardiovascular and metabolic health outcomes.

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