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ORIGINAL ARTICLE

Clinical Trials and Investigations

Impact of lifestyle moderate-to-vigorous physical activity timing on glycemic control in sedentary adults with overweight/obesity and metabolic impairments

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Abstract

Objective: Moderate-to-vigorous physical activity (MVPA) improves glucose levels; however, whether its timing affects daily glycemic control remains unclear. This study aims to investigate the impact of lifestyle MVPA timing on daily glycemic control in sedentary adults with overweight/obesity and metabolic impairments.

Methods: A total of 186 adults (50% women; age, 46.8 [SD 6.2] years) with overweight/obesity (BMI, 32.9 [SD 3.5] kg/m^2) and at least one metabolic impairment participated in this cross-sectional study. MVPA and glucose patterns were simultaneously monitored over a 14-day period using a triaxial accelerometer worn on the nondominant wrist and a continuous glucose-monitoring device, respectively. Each day was classified as "inactive" if no MVPA was accumulated; as "morning," "afternoon," or "evening" if >50% of the MVPA minutes for that day were accumulated between 0600 and 1200, 1200 and 1800, or 1800 and 0000 hours, respectively; or as "mixed" if none of the defined time windows accounted for >50% of the MVPA for that day.

Antonio Clavero-Jimeno and Manuel Dote-Montero contributed equally.

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Results: Accumulating >50% of total MVPA during the evening was associated with lower 24-h (mean difference [95% CI], −1.26 mg/dL [95% CI: −2.2 to −0.4]), diurnal (−1.10 mg/dL [95% CI: −2.0 to −0.2]), and nocturnal mean glucose levels (−2.16 mg/dL [95% CI: −3.5 to −0.8]) compared with being inactive. This association was stronger in those participants with impaired glucose regulation. The pattern of these associations was similar in both men and women.

Conclusions: These findings suggest that timing of lifestyle MVPA is significant. Specifically, accumulating more MVPA during the evening appears to have a beneficial effect on glucose homeostasis in sedentary adults with overweight/obesity and metabolic impairments.

INTRODUCTION

Obesity is closely associated with cardiometabolic disorders, particularly insulin resistance and type 2 diabetes mellitus [1–3]. Healthy dietary patterns and physical activity (PA) are presented as the first-line treatment to reduce body weight and improve glucose control in individuals with obesity. Preliminary evidence has suggested that the timing of moderate-to-vigorous PA (MVPA) may exert a significant influence on glucose levels [4–8].

Human physiological processes such as glucose metabolism are intricately regulated by circadian rhythms. Diurnal variations have been observed in blood glucose and insulin concentration, with higher levels in the morning compared with the evening [9, 10]. Furthermore, during the afternoon and evening, skeletal muscle exhibits reduced efficiency in glucose uptake, leading to diminished insulin responsiveness [11]. Accumulating MVPA during the afternoon and evening holds the potential to provide additional benefits for enhancing glucose homeostasis [11–13]. Previous trials have demonstrated that afternoon and evening exercise sessions are more effective than morning sessions at improving nocturnal glucose levels [14] and glycated hemoglobin (HbA1c) [15]. However, adherence to planned exercise sessions in individuals with obesity is low, and the PA that these individuals accumulate naturally as part of their daily life becomes a factor of interest.

Despite major advances in the area, the constraints observed in prior studies restrict the generalizability and practical implementation of their findings. First, none of the previous studies on the timing of lifestyle PA, to our knowledge, has investigated its associations with glucose levels during the diurnal and nocturnal periods. Second, previous studies have predominantly focused on glucose levels during fasting conditions [4], despite the fact that individuals spend the majority of their day in a postprandial state [16]. Therefore, the use of continuous glucose-monitoring (CGM) devices becomes indispensable in the assessment of glycemic control because they provide detailed information on 24-h mean glucose levels [17]. Third, previous investigations have classified lifestyle PA timing at a person level [4, 7, 18]; however, the timing of lifestyle PA may vary across the days because it is accumulated naturally, without any previous planning, as opposed to exercise sessions that are planned and follow a consistent schedule. Therefore, the same individual may register days with morning timing and evening timing during the week, and this variation should be accounted for when investigating the associations of lifestyle PA timing with health outcomes. Finally, prior investigations have predominantly centered on men or have combined both men and women in their analyses, despite women generally exhibiting greater insulin sensitivity than men [19]. This underscores the significance of considering sex-specific differences in glucose levels and emphasizes the necessity to conduct separate analyses for men and women [20].

Study Importance

What is already known?

- It has been well established that moderate-to-vigorous physical activity (MVPA) enhances glucose homeostasis in adults with overweight/obesity who are at higher risk of developing insulin resistance.
- However, little is known regarding the optimal timing of MVPA to improve daily glucose control.

What does this study add?

- Accumulating most lifestyle MVPA in the evening is associated with lower glucose levels in adults with overweight/obesity. Moreover, this association seems to be further enhanced in those with impaired glucose regulation.

How might these results change the direction of research?

- We show that not only the quantity but also the timing of lifestyle MVPA is relevant when enhancing glucose homeostasis.
- Further research should focus on whether these results might be applicable to older adults or individuals with diabetes because they need to maintain an optimal glycemic control to ensure their overall health status and well-being.

Therefore, the objective of the present study was to investigate the associations between the timing of lifestyle MVPA and glycemic control (i.e., 24-h, diurnal, and nocturnal mean glucose levels) in adults with overweight/obesity and metabolic impairments. We hypothesized that accumulating most MVPA during the afternoon and/or evening would be likely associated with lower 24-h, diurnal, and nocturnal mean glucose levels.

METHODS

Study design

This study used data from the baseline examinations of the EXTREME project, a multicenter randomized controlled trial conducted in Granada (southern Spain) and Pamplona (northern Spain) (ClinicalTrials.gov identifier: NCT05310721). The study design was approved by the Ethics Committees of each center (Andalusian Health Service, Provincial Research Ethics Committee of Granada, and the Clinical Research Ethics Committee of Navarra, PI_2021/119). The aim of the EXTREME project was to study the efficacy and feasibility of time-restricted eating on visceral adipose tissue (primary outcome), body composition, and cardiometabolic risk factors in adults with overweight/obesity. Further information regarding the study design can be found elsewhere [21]. During a 2-week lead-in period prior to the beginning of the intervention, participants were instructed to simultaneously wear an accelerometer and a CGM device during 14 consecutive days.

Participants

Potential participants were recruited from April 11, 2022, to December 5, 2022, with a study completion date of March 6, 2023. Inclusion criteria were as follows: 1) aged 30 to 60 years; 2) body mass index (BMI) between 25.0 and 40.0 kg/m^2 and waist circumference ≥ 95.0 cm in men and ≥82.0 cm in women; 3) body weight stability (within 3% of screening weight) for >3 months before the study; 4) reported being inactive (<150 min/wk of MVPA) for >3 months prior to study entry; 5) habitual eating window ≥ 12 h; and 6) having at least one of the following metabolic impairments: high blood pressure (defined as systolic blood pressure > 130 mm Hg and diastolic blood pressure > 85 mm Hg), high low-density lipoprotein (>100 mg/dL) or low high-density lipoprotein cholesterol levels (<50 mg/dL for women and <40 mg/dL for men), high serum triglycerides concentration (>150 mg/dL), and impaired fasting glucose levels (defined as fasting plasma glucose levels ≥ 100 mg/dL and ≤125 mg/dL, HbA1c between ≥5.7% and <6.5%, or insulin resistance, assessed by homeostasis model assessment of insulin resistance [HOMA-IR] >2.5). Exclusion criteria were as follows: 1) medical history with an adverse cardiovascular event; 2) having a disease in which fasting is contraindicated; 3) taking any medications that could modify glucose metabolism; 4) active abuse of tobacco or alcohol consumption; 5) being enrolled in a fasting or weight loss program; 6) working night shifts or having continuous sleep disruptions; and 7) traveling over different time zones during the study period.

Measurements

Height and body weight were measured while participants were barefoot and wearing light clothing with a stadiometer and a scale (SECA model 799, Electronic Column Scale, Seca GmbH, Hamburg, Germany). We calculated BMI by dividing body weight in kilograms by height in meters squared. Fat mass percentage and fat-free mass were assessed using a dual-energy x-ray absorptiometry scan, i.e., the Hologic QDR-4500 W in Granada and the Hologic Horizon-WI (Hologic Inc., Bedford, Massachusetts) in Pamplona.

PA was objectively monitored using a triaxial accelerometer (ActiGraph GT3X+, ActiGraph LLC, Pensacola, Florida). The accelerometers were initialized to collect raw accelerations at a frequency of 100 Hz, and participants wore the device on their nondominant wrist. This equipment was configured to measure for 14 consecutive days (24 h/day). In addition, participants were instructed to register bedtime and wake-up time every day in a mobile phone application specifically designed for the study (com.nnbi.app_extreme_granada; NNBi2020 S.L., Navarra, Spain). When the 2-week lead-in period finished, raw data from accelerometers were downloaded using the ActiLife software (ActiGraph LLC), and the raw data were processed with the open-source GGIR R package [22]. In brief, the Euclidean Norm of the raw accelerations Minus One (ENMO) G with negative values rounded to zero was calculated over 5-s epochs; non-wear time periods were identified from the magnitude and variability of the raw accelerations measured at each accelerometer axis [23] and imputed when appropriate by the average ENMO at the same time interval during the rest of the recording days; and sleep and awake periods were identified using an automated algorithm based on the variability of the arm posture and guided by the sleep times reported by the participants [23, 24]. Then, MVPA was classified when ENMO during the awake time was ≥100 mg in bouts of at least 5 min (with an allowance of 20% of the time below the threshold) [25]. As participants reported being inactive, the MVPA assessed was considered to be lifestyle MVPA.

Subsequently, we classified each day based on MVPA volume as follows: "inactive" (i.e., 0 min/day of MVPA); "somewhat active" (i.e., 0–21.4 min/day of MVPA); "active" (i.e., 21.4–42.9 min/day of MVPA); and "very active" (i.e., >42.9 min/day of MVPA), based on the goal of meeting the World Health Organization (WHO) guidelines on physical activity scaled from minutes per week to minutes per day [26]. Additionally, we classified each day based on the timing as follows: inactive (i.e., no MVPA); morning (i.e., 0600–1200 hours); afternoon (i.e., 1200–1800 hours); evening (i.e., 1800–0000 hours); or mixed (i.e., not a clear timing for MVPA). For that, we quantified the proportion of the total lifestyle MVPA that occurred within each of the windows and, if more than 50% of the total MVPA for a given day was accumulated in any of the windows, we then classified that day as predominantly "morning," "afternoon," or "evening," respectively.

If any of the windows had >50% of MVPA of the day, there was not a clear predominant window, and we classified the day as mixed. This allowed us to perform a day-level and within-participant analysis of how the lifestyle MVPA timing impacts glycemic control.

Participants' daily glucose levels were measured using a CGM device (FreeStyle LibrePro in Granada and FreeStyle Libre 2 in Pamplona, Abbot Laboratories, Chicago, Illinois) for 14 days. These CGM models store averages of interstitial glucose every ~15 min, which provides approximately real-time glucose data [17]. The CGM device data were time-matched with the accelerometer data to allow for the calculation of the mean glucose over the diurnal and nocturnal windows. That is, we applied the accelerometer-derived sleep onset and wake-up times to calculate the mean glucose over the full day (namely the 24-h mean glucose), the waking hours (diurnal mean glucose), and the sleeping hours (nocturnal mean glucose) for each participant's day. The criteria to consider a valid day were as follows: 1) the CGM devices should have registered data for at least 70% of the entire day (i.e., more than 67 recordings in a day considering a 15-min sampling frequency) [17]; and 2) participants should have worn the accelerometers for at least 16 h of the day, with at least 3 valid hours registered in each one of the predefined windows (i.e., morning, afternoon, and evening). Additionally, only those windows with at least 3 h classified as awake time were included.

Statistical analysis

Data were expressed as mean (SD) and confidence interval (CI), unless otherwise stated. All outcome variables were checked for normality with visual inspection of histograms. We detected an outlier presenting mean glucose levels above 4 SDs from the group mean, and, after double-checking the CGM data, we decided to exclude the participant from the analysis. We investigated potential interactions for age group (i.e., age <45 vs. ≥45 years), study site (i.e., Granada vs. Pamplona), and sex in the association of lifestyle MVPA volume and MVPA timing with glycemic control (i.e., 24-h, diurnal, and nocturnal mean glucose) using linear mixed models fitting the participants' identifiers as random intercepts, the MVPA volume or timing and the interaction terms as fixed factors, and the mean glucose over each window as outcome. No evidence of interaction was observed.

First, we performed linear mixed models to compare the total daily time accumulated in MVPA across the lifestyle MVPA timing groups (i.e., inactive, morning, afternoon, evening, and mixed). Second, we fitted the 24-h, diurnal, and nocturnal mean glucose as outcomes; the lifestyle MVPA volume or timing groups as fixed factors; and the participants' identifiers as random intercepts in linear mixed models to investigate the association of lifestyle MVPA volume and timing with mean glucose levels during the whole day and during the diurnal and nocturnal windows. Then, we conducted a secondary analysis within a subgroup of participants characterized by impaired glucose regulation, as determined by the presence of any of the following criteria: fasting plasma glucose levels between ≥100 and ≤125 mg/dL; HbA1c levels ranging from ≥5.7% to <6.5%; or insulin resistance, as indicated by HOMA-IR > 2.5. We also conducted sensitivity analyses excluding those participants without inactive days and excluding those participants with 6 or fewer valid days to ensure the robustness of the results. Fixed effects (within-participant differences) with their 95% CI are presented. All statistical analyses and figures were performed in R version 4.3.0 (https://cran.r-project.org/, The R Project for Statistical Computing, Vienna, Austria).

RESULTS

Table 1 shows descriptive data of the study participants. A total of 186 adults (50% women; mean [SD] age, 46.8 [6.2] years) with overweight/obesity (BMI, 32.9 [3.5] kg/m^2) and metabolic impairments were included in this study. These participants provided a mean of 10.0 (3.2) days of valid data from accelerometers and CGM devices, and 80% had 8 or more valid days. The CGM devices collected data for 90% of the day in 83% of the days included in the analysis. Table S1 displays the days categorized for each participant across the different time windows. Mean values of MVPA were 24.0 (21.5) min/day. There were no statistically significant differences in the total mean volume of MVPA across the morning (25.6 [95% CI: 22.2–29.1] min), afternoon (26.7 [95% CI: 23.4–30.0] min), and evening days (30.4 [95% CI: 26.9–34.0] min), whereas participants accumulated significantly more MVPA on the mixed days (43.8 [95% CI: 38.4–49.2] min) compared with any of the other timing groups (all $p < 0.001$; Figure 1).

Overall, we observed that participants showed lower 24-h, diurnal, and nocturnal mean glucose levels during the days on which they performed some activity compared with their inactive days (Figure 2). Specifically, 24-h mean glucose was broadly 1.0 mg/dL lower during the somewhat active days (−0.95 [95% CI: −1.70 to −0.20]) and 1.5 mg/dL lower during the very active days (−1.48 [95% CI: −2.44 to −0.52]) compared with the inactive days. Similar differences were observed for the diurnal mean glucose, and there were slightly higher differences for the nocturnal mean glucose, in which the differences surpassed 1.5 mg/dL for the three active categories: somewhat active (−1.54 [95% CI: −2.67 to −0.40]); active (−1.64 [95% CI: −2.99 to −0.28]); and very active (−1.69 [95% CI: −3.13 to −0.25]). Moreover, sensitivity analyses showed similar results when excluding those participants without inactive days (Figure S1) and when excluding those participants with 6 or fewer valid days (Figure S2).

Twenty-four–hour (−1.28 [95% CI: −2.16 to −0.40] mg/dL; $p = 0.004$), diurnal (−1.10 [95% CI: −2.02 to −0.18] mg/dL; $p = 0.020$), and nocturnal (−2.14 [95% CI: −3.47 to −0.81] mg/dL; $p = 0.002$) mean glucose levels were lower when most of the MVPA was accumulated during the evening compared with the inactive days (Figure 3). Additionally, 24-h (−0.98 [95% CI: −1.80 to −0.16] mg/dL; $p = 0.019$) and nocturnal (−1.72 [95% CI: −2.96 to −0.47] mg/dL; $p = 0.007$) mean glucose levels, but not diurnal mean glucose levels (−0.76 [95% CI: −1.63 to 0.10] mg/dL; $p = 0.083$), were lower in afternoon days than in inactive days (Figure 3). Otherwise, days on which PA was accumulated during the morning or spread out over different windows (i.e., mixed) did

TABLE 1 Descriptive characteristics of the participants.

	All ($N = 186$)	Men ($n = 93$)	Women ($n = 93$)
Age (y)[a]	46.8 (6.2)	47.2 (6.5)	46.5 (6.0)
Body weight (kg)[a]	94.9 (14.9)	102.1 (14.3)	87.6 (11.5)
Height (cm)[a]	169.5 (9.0)	176.4 (6.4)	162.7 (5.2)
BMI (kg/m^2)[a]	32.9 (3.5)	32.7 (3.3)	33.1 (3.7)
Fat-free mass (kg)[a]	54.7 (11.3)	63.8 (7.6)	45.8 (5.8)
Fat mass (kg)[a]	39.3 (8.1)	37.4 (8.3)	41.2 (7.5)
Fat mass (%)[a]	42.0 (6.8)	36.7 (4.4)	47.2 (4.3)
24-h mean glucose (mg/dL)[a]	105.6 (10.0)	108.3 (10.3)	103.0 (9.0)
Nocturnal mean glucose (mg/dL)[a]	107.2 (9.8)	109.8 (10.2)	104.7 (8.7)
Diurnal mean glucose (mg/dL)[a]	101.5 (11.7)	104.4 (11.9)	98.7 (10.8)
Moderate-to-vigorous PA (min/d)[a]	24.0 (21.5)	25.1 (22.6)	22.9 (20.3)
Metabolic impairments (%)[a]	3.0 (1.5)	3.3 (1.5)	2.8 (1.5)
High systolic blood pressure (%)[b]	57 (31)	39 (42)	18 (19)
High diastolic blood pressure (%)[b]	56 (30)	34 (37)	22 (24)
High LDL cholesterol (%)[b]	160 (86)	81 (87)	79 (85)
Low HDL cholesterol (%)[b]	38 (20)	12 (13)	26 (28)
High TG (%)[b]	49 (26)	31 (33)	18 (19)
Impaired fasting glucose (%)[b]	44 (24)	29 (31)	15 (16)
Impaired HbA1c levels (%)[b]	29 (16)	15 (16)	14 (15)
Impaired HOMA-IR (%)[b]	86 (46)	46 (49)	40 (43)

Note: [a]Data are presented as mean (SD). [b]Data are presented as frequency (associated percentage). Metabolic impairments included the following: high blood pressure (defined as systolic blood pressure > 130 mm Hg and diastolic blood pressure > 85 mm Hg), high LDL cholesterol levels (>100 mg/dL) or low HDL concentrations (<50 mg/dL for women and <40 mg/dL for men), high serum TG concentration (>150 mg/dL), impaired fasting glucose levels (defined as fasting plasma glucose levels ≥ 100 mg/dL and ≤125 mg/dL, HbA1c between ≥5.7% and <6.5%, or insulin resistance, measured by HOMA-IR >2.5). Abbreviations: HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; PA, physical activity; TG, triglycerides.

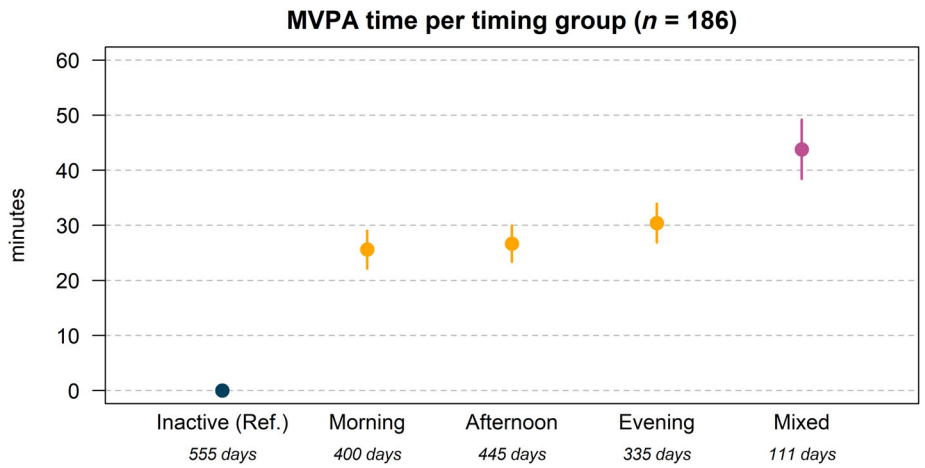

FIGURE 1 Time accumulated in lifestyle moderate-to-vigorous physical activity (MVPA) across days classified based on the PA timing (i.e., inactive, morning, afternoon, evening, mixed). Dots represent the fixed effect and error bars the 95% CI based on mixed model analysis. [Color figure can be viewed at wileyonlinelibrary.com]

not show statistically different glucose levels than the inactive days. The pattern of these associations was similar in both men and women. Furthermore, sensitivity analyses showed similar results when excluding those participants without inactive days (Figure S3) and when excluding those participants with 6 or fewer valid days (Figure S4).

Secondary analyses in participants with impaired glucose regulation revealed that 24-h (−2.15 [95% CI: −3.29 to −1.01] mg/dL; $p < 0.001$), diurnal (−1.62 [95% CI: −2.84 to −0.41] mg/dL; $p = 0.009$), and nocturnal (−3.68 [95% CI: −5.42 to −1.94] mg/dL; $p < 0.001$) mean glucose levels were lower when most of the MVPA was

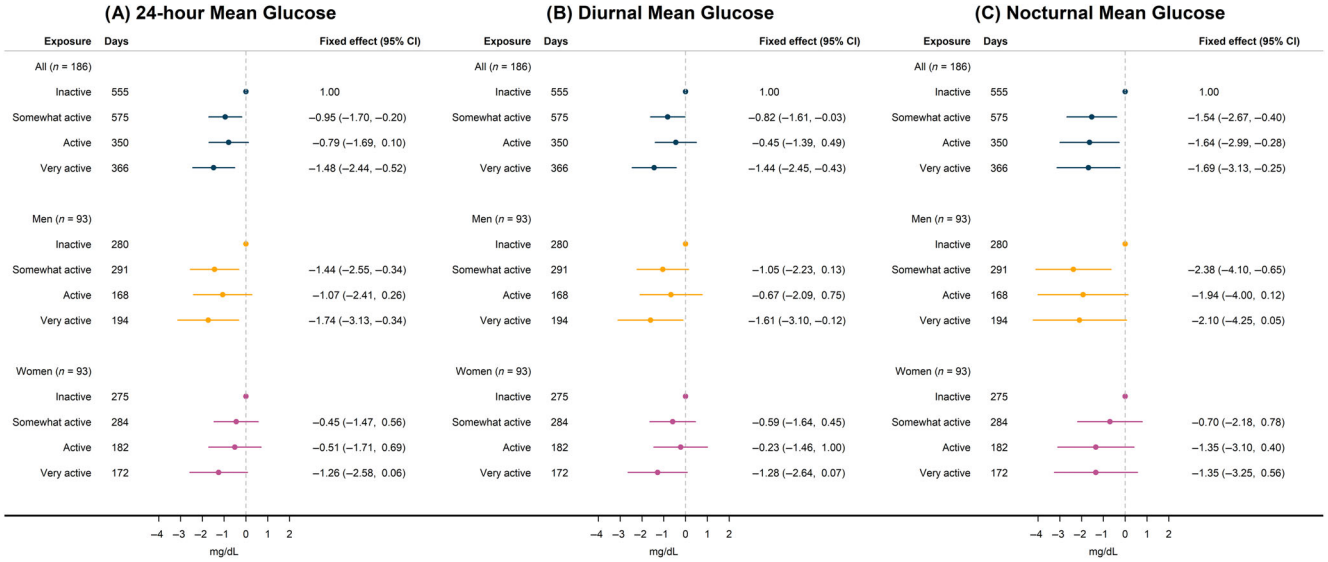

FIGURE 2 (A) Twenty-four-hour, (B) diurnal, and (C) nocturnal mean glucose levels across days classified based on lifestyle moderate-to-vigorous physical activity (MVPA) volume (i.e., inactive, somewhat active, active, and very active based on the World Health Organization's guidelines for physical activity) in the whole analytical sample and separately in men and women. The days classified as inactive are considered the reference. Fixed effects with their 95% CI are presented based on mixed model analysis. [Color figure can be viewed at wileyonlinelibrary.com]

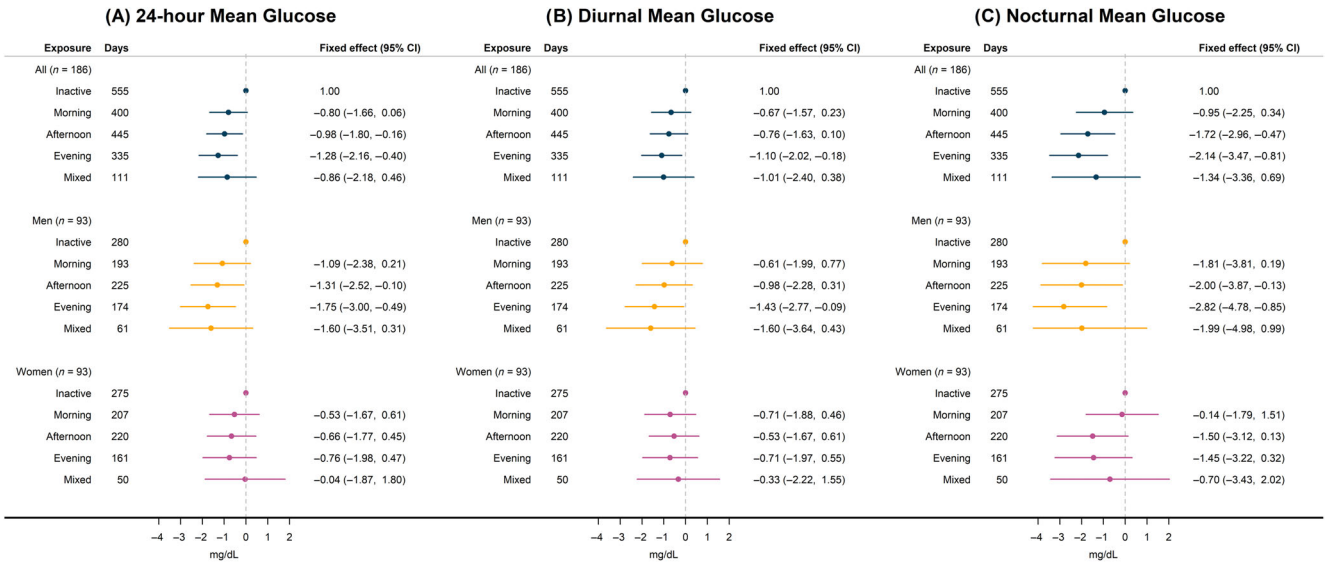

FIGURE 3 (A) Twenty-four-hour, (B) diurnal, and (C) nocturnal mean glucose levels across days classified based on lifestyle moderate-to-vigorous physical activity (MVPA) timing (i.e., inactive, morning, afternoon, evening, and mixed) in the whole analytical sample and separately in men and women. The days classified as inactive are considered the reference. Fixed effects with their 95% CI are presented based on mixed model analysis. [Color figure can be viewed at wileyonlinelibrary.com]

accumulated during the evening compared with the inactive days, showing stronger association between the timing of lifestyle MVPA and glycemic control (Figure 4). We repeated the analysis by each criterion separately, and results remained similar (impaired fasting plasma glucose levels in Figure S5, HbA1c in Figure S6, and HOMA-IR in Figure S7).

DISCUSSION

The results of this study demonstrate that accumulating most lifestyle MVPA during the evening is associated with lower 24-h, diurnal, and nocturnal mean glucose levels in sedentary adults with overweight/obesity and metabolic impairments. These associations are further

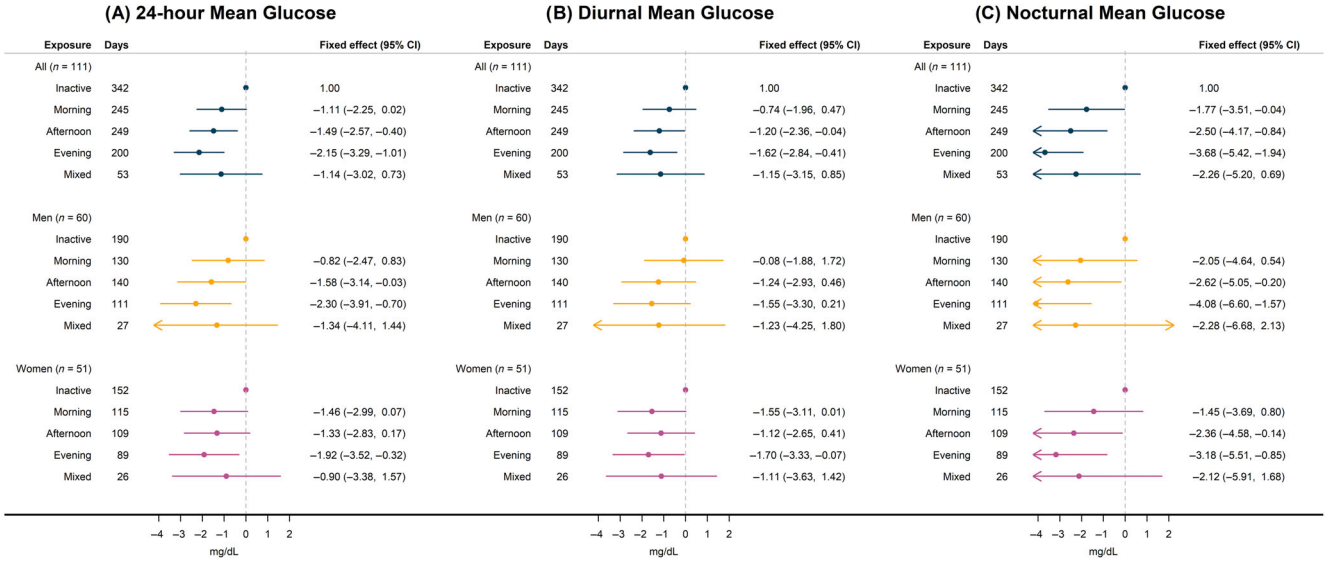

FIGURE 4 (A) Twenty-four-hour, (B) diurnal, and (C) nocturnal mean glucose levels across days classified based on lifestyle moderate-to-vigorous physical activity (MVPA) timing (i.e., inactive, morning, afternoon, evening, and mixed) in the participants exhibiting fasting glucose metabolism impairment (i.e., impaired fasting plasma glucose levels between ≥100 and ≤125 mg/dL, glycated hemoglobin levels ranging from ≥5.7% to <6.5%, or insulin resistance, as indicated by a homeostasis model assessment of insulin resistance [HOMA-IR] score > 2.5) and separately in men and women. The days classified as inactive are considered the reference. Arrows indicate that the interval extends beyond the values represented on the axis. Fixed effects with their 95% CI are presented based on mixed model analysis. [Color figure can be viewed at wileyonlinelibrary.com]

enhanced in those participants with impaired glucose regulation, consistent with previous findings [4, 14]. Additionally, the data reveal that meeting the MVPA recommendations (i.e., 150–300 min/wk of MVPA) is associated with improved glycemic control compared with being inactive. These results underscore the significance of not only the volume but also the timing of lifestyle MVPA in enhancing glycemic control.

Our findings concur with previous studies that have assessed glucose levels in fasting conditions and using CGM devices. One cross-sectional study showed that adults with overweight/obesity (58% women) who performed most of their MVPA in the afternoon or evening had reduced insulin resistance (i.e., lower HOMA-IR) compared with accumulating most of their MVPA in the morning or following a mixed distribution [4]. Likewise, previous exercise-based studies have shown that evening exercise, as opposed to morning, can lead to higher benefits on glycemic control (i.e., lower HbA1c, 24-h, and nocturnal mean glucose levels) in adults with type 2 diabetes and with obesity and impaired fasting glucose levels [15, 27, 28]. Moreover, a randomized clinical trial conducted in 24 middle-aged men with obesity observed that evening high-intensity interval training induced lower nocturnal mean glucose levels than morning exercise [14]. Similarly, Kim et al. showed that late-afternoon endurance exercise was more effective when improving 24-h mean glucose than morning exercise in men [29].

The specific mechanisms responsible for the potential benefits of lifestyle MVPA timing on glycemic control in individuals with overweight/obesity are still unclear. It has been suggested that skeletal muscle tends to exhibit less efficiency in glucose uptake and decreased insulin sensitivity during the evening due to the circadian oscillations [11]. Therefore, evening MVPA may enhance substrate use (e.g., glucose), improving the glucose uptake by skeletal muscle [8, 11, 13]. Exercise has proven to be a regulator of the body's internal clock, influencing clock genes within skeletal muscle [30, 31]. These genes play a significant role in skeletal muscle metabolism and glucose clearance, particularly through the activation of 5′-adenosine monophosphate-activated protein kinase (AMPK) [32]. Furthermore, exercise exerts insulin-sensitizing effects by facilitating glucose transporter type 4 (GLUT-4) translocation, a process mediated by AMPK [33].

Consistent evidence has revealed the existence of a diurnal rhythm in glucose tolerance and insulin sensitivity because these functions are relatively impaired in the evening compared with the morning [9]. Regarding populations with type 2 diabetes, morning exercise may generate a higher risk of hyperglycemia episodes because high cortisol levels may induce elevated glucose concentrations during this time of the day [34]. On the contrary, this pattern indicates a higher potential for reducing glucose levels when engaging in evening exercise compared with morning exercise, which concur with the findings of the present study. We observed lower 24-h, diurnal, and nocturnal mean glucose levels in those days in which participants performed most of their lifestyle MVPA in the evening. The absence of evidence regarding sex interaction in the relationship between MVPA volume and timing with glycemic control is noteworthy. Additionally, the similarity in the patterns of these associations among men and women found in the present study implies that both sexes could derive benefits from accumulating more MVPA during the evening.

The study has several limitations, including the observational design, which prevents establishing causal relationships. We do not know whether these findings can be extrapolated to older adults or individuals with diabetes. Additionally, we cannot determine the exact

extent of variance resulting from both the technical errors inherent in the CGM device and the day-to-day variability. Moreover, the observational day-level design is not able to fully ascertain how the MVPA levels from the previous day might impact the glucose levels of the day after. Of note, we were unable to assess the dietary intake or the levels of stress during the study period. These factors are recognized to impact glycemic control [8], and their absence in our assessment could have influenced our results. However, it is noteworthy that our results were further enhanced when we conducted sensitivity analyses on participants with impaired glucose regulation, which bolsters our confidence in the validity and consistency of the present results. Although the effect size observed in mean glucose levels may be relatively modest, it is essential to consider that the participants in this study reported to have a sedentary lifestyle, which was confirmed with the accelerometer data. Therefore, it is to be expected that the impact of both PA volume and timing on glycemic control is amplified in populations with higher activity levels. Strengths of our study include employing objective assessment of MVPA over a 14-day, 24-h/day period using accelerometry, complemented by simultaneous CGM devices. We performed a day-level and within-participant analysis, diminishing the possible influence of biological, physiological, and behavioral factors and enabling a more precise assessment, taking into account individuals' biological rhythms [35]. Unlike some previous studies that have been imbalanced in terms of sex, this study includes both men and women as well as sex-specific analyses of the results.

CONCLUSION

The present study shows that the timing of lifestyle MVPA is significant and that accumulating most MVPA during the evening is associated with lower glucose levels in adults with overweight/obesity and metabolic impairments. Of note is that these associations are strengthened in individuals with impaired glucose regulation. Additionally, the data suggest that meeting the MVPA recommendations is associated with improved glycemic control compared with being inactive. These findings highlight the promising area of MVPA timing as a novel approach to improve metabolic health in people at risk of developing cardiovascular diseases.O

AUTHOR CONTRIBUTIONS

The authors' responsibilities were as follows: Antonio Clavero-Jimeno, Manuel Dote-Montero, Jairo H. Migueles, Idoia Labayen, and Jonatan R. Ruiz designed the study; Antonio Clavero-Jimeno, Manuel Dote-Montero, Alba Camacho-Cardenosa, Maddi Oses, Jon Echarte Medina, and Juan M. A. Alcantara collected the data; Jairo H. Migueles, Antonio Clavero-Jimeno, Manuel Dote-Montero, and Jonatan R. Ruiz analyzed the data; Antonio Clavero-Jimeno, Manuel Dote-Montero, and Jonatan R. Ruiz wrote the original draft; Antonio Clavero-Jimeno, Manuel Dote-Montero, Jairo H. Migueles, Alba Camacho-Cardenosa, Maddi Oses, Jon Echarte Medina, Juan M. A. Alcantara, Manuel Muñoz-Torres, Idoia Labayen, and Jonatan R. Ruiz critically revised the manuscript and discussed the results; Antonio Clavero-Jimeno, Manuel Dote-Montero, and Jonatan R. Ruiz were primarily responsible for the final content; and all authors read and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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