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ORIGINAL RESEARCH

# The Association of the Timing of Physical Activity with Cardiometabolic Health in Diabetes: An IMI2 SOPHIA Study

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**Purpose:** This study aimed to investigate the association of timing of the most active five hours (M5 time) with markers of cardiometabolic health in people with type 1 diabetes (T1D) and type 2 diabetes (T2D).

**Patients and Methods:** People with T1D or T2D were invited to participate in the study. Physical activity was measured over a 7-day period with a wrist worn accelerometer. The M5time (as a linear and circular (sin-cos) variable) and the amount of activity in these five hours (M5value) were calculated, and associations with glycaemic control, blood lipids and body composition were examined using multiple linear regression, with multiple testing controlled using false discovery rate (FDR) correction.

**Results:** A total of 891 people with T1D and 1381 people with T2D were included. In people with T1D, M5time (linear) was associated with waist circumference after full adjustment (model 3) (B = −0.32, SE = 0.15, FRD p = 0.047). Similarly, in people with T1D M5 time (circular) was also significantly associated with BMI (p = 0.004) and waist circumference (p = 0.001), with amplitudes of BMI: 1.32 kg/m2 and Waist: 4.28 cm, and phases of BMI: 12:51h and Waist: 13:06h. In people with T2D, M5 time was not associated with any cardiometabolic markers after FDR correction in any adjusted models.

**Conclusion:** In people with T1D, the time of day at which people were most active was associated with some cardiometabolic markers. However, in people with T2D, there was no association with any cardiometabolic markers. Overall, our data indicates little effect of time of and physical activity at any time of day should be promoted.

**Keywords:** type 1 diabetes, type 2 diabetes, physical activity, timing, circadian

## Introduction

Diabetes is a global pandemic, affecting 537 million people worldwide.[1] In the Middle East and North Africa region, 73 million adults are living with diabetes with approximately 25% of adults living with diabetes in Kuwait.[1] Diabetes has several consequences including an increased risk of vascular diseases, such as, neuropathy, nephropathy, retinopathy, cerebrovascular disease, and peripheral arterial disease.[2–4] Among these, cardiovascular disease (CVD) is highly prevalent in people with diabetes and a major cause of mortality.[5] This risk is a particular issue when diabetes onset occurs at a younger age.[6,7] For example, in people with type 1 diabetes (T1D), CVD contributes to a reduction in life expectancy by at least 11 years.[8] Several reasons account for this increase in CVD risk including the presence of hyperlipidaemia, obesity,

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hyperglycaemia, hypertension, oxidative stress, chronic inflammation and endothelial dysfunction.[9–11] Therefore, identifying the effective strategies to mitigate the elevated cardiovascular risk in people with diabetes is of the utmost importance.

Physical activity is pivotal in diabetes management and prevention of CVD. Regular physical activity (ie. 150 minutes of moderate-to-vigorous activity and 2–3 sessions per week of resistance exercise) is recommended for people living with diabetes.[12] Numerous studies have demonstrated the benefits of physical activity in people with diabetes, with increases in muscle mass and strength, enhanced insulin responsiveness, and improvements in blood pressure, lipid profiles, blood glucose control and body composition.[13–17] However, beyond the total volume of physical activity beneficial, there is emerging evidence suggesting that the timing of physical activity may influence the cardiometabolic benefits through coordination with circadian rhythms.[18,19]

For example, data from 92,139 people, from the general population, in the UK biobank showed that physical activity in the morning and afternoon, but not the evening, was associated with a lower risk of CVD and all-cause mortality.[20] In contrast, a recent systematic review found no consistent effect of timing of physical activity on body composition, or cardiometabolic and disease outcomes.[21] These discrepant findings highlight uncertainty in the literature and suggest that the influence of activity timing may vary across populations and metabolic states. Data in people with diabetes is limited with findings mixed. For example, in people with type 2 diabetes (T2D), exercise performed in the afternoon is more effective at reducing acute blood glucose levels compared to the morning.[22,23] These findings are supported by similar work.[24,25] Conversely, other studies have reported no effects of time of day on the metabolic benefits of physical activity in T2D.[26] The reasons for these differences are unknown, but this data highlights the uncertainty in this area. There is less data looking at longer term cardiometabolic outcomes in people with T1D, but acute data indicates a more pronounced hyperglycaemic response to exercise in the morning compared to the afternoon.[27,28] Although, whether habitual timing of physical activity is associated with more favourable cardiometabolic profiles in people with T1D or T2D remains largely unexplored.

Therefore, it is possible that the timing at which peak physical activity is performed during the day may be associated with measures of cardiometabolic health, but data in people with diabetes, particularly T1D, is currently limited and equivocal. The aim of this study was to investigate the association of timing of peak physical activity with markers of cardiometabolic health in people with T1D or T2D. A secondary aim was to investigate the association of the amount of physical activity during peak physical activity with markers of cardiometabolic health in people with T1D or T2D.

# Materials and Methods

## Study Setting and Participants

This is a cross-sectional study, conducted among people with T1D or T2D diabetes aged ≥18 years, attending clinics or participating in ongoing research at the Dasman Diabetes Institute in Kuwait, from 2022 to 2024. During a study visit demographic and clinical data were collected, and participants were given an accelerometer to wear for the following 7 days. The study details were thoroughly explained both verbally and in writing, and participants provided written informed consent. Approval for the study was obtained from the Dasman Diabetes Institute Ethical Review Committee, and it adhered to the guidelines outlined in the Declaration of Helsinki.

## Demographics

Age was calculated from participants' date of birth, clinical history recorded, and measurements of body mass, height, BMI and waist circumference were taken. Data such as HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were collected from electronic health records.

## Accelerometer

Following the collection of demographics, participants were provided with a GENEActiv original accelerometer and instructed to wear it continuously for 24 hours a day over a 7-day period.[29] A valid day was defined as having >16 h of data in it, and we excluded participants with less than 3 valid days of data or if wear data were not present for each 15-min period of the 24-h cycle. The accelerometer was set to record at 100 Hz. Data extraction and processing were performed using GGIR package with the timing of the most active 5 hours (M5time, expressed in hours:minutes) and the

acceleration value (ie. physical activity levels) during that 5 hours (M5value, expressed in milligravities) quantified.[30] We also quantified the overall physical activity using the mean acceleration across the day the Euclidean Norm Minus One (ENMO variable) measured in mg. The collected acceleration data were calibrated to local gravity using the methods established by van Hees et al.[31]

## Circular Modeling of Time-of-Day

Because clock time is periodic, we modeled M5time as a circular predictor via first-order Fourier terms: $\sin(2\pi \cdot \text{time}/24)$ and $\cos(2\pi \cdot \text{time}/24)$. We assessed its overall effect using a joint Wald test of both coefficients (H0: $\beta_{sin} = \beta_{cos} = 0$) and summarized the magnitude and timing via amplitude and phase, transformed to peak time (hours) on [0,24). For interpretability, we also ran linear models using M5time as a continuous hour variable. This approach to circular predictors and inference is standard in chronobiology and biostatistics.

## Statistical Analysis

General demographics and physical activity descriptive data are presented as mean (SD), with data stratified by diabetes type and in by being most active in morning (M5 time before 12noon) or afternoon (M5 time after 12noon). Multiple linear regression analysis was employed to investigate the association of M5value and M5time (modelled as linear and circular (sin-cos)) with HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, waist circumference and BMI (outcome). For circular variable construction, we replace the single linear term with the pair $\sin(2\pi \cdot \text{M5time}/24)$ and $\cos(2\pi \cdot \text{M5time}/24)$, which captures the 24 h periodic nature of clock time and prevents edge artifacts at midnight. Significance for these models was assessed using a joint Wald test for both terms. Multiple testing was controlled using false discovery rate (FDR) by the Benjamini–Hochberg method. We provide exact p-values for the joint circular tests (sin/cos) and the q-value for each individual parameter estimate. Models included an unadjusted model (Model 1) and an adjusted model accounting for sex, age, duration of diabetes, smoking status, comorbidities and medications (insulin, glucose-lowering and lipid-lowering medications) (Model 2) and Model 2 adjustment with overall physical activity (Model 3). Assumptions of linear regression were tested, with all models meeting these assumptions. To justify our adjustment models, we have generated a directed acyclic graph (Supplementary Figures 1). We also stratified our samples into people whose peak physical activity time occurred in the morning or afternoon (before or after 12 noon) and compared cardiometabolic profiles between these groups. All analyses were performed using R (version 2023.12.1+402).

# Results

The current study included a total of 891 people with T1D and 1381 people with T2D with their baseline characteristics presented in Table 1. In people with T1D, 49.3% (n = 439) were male, with a mean age of 34.4 ± 10.1 years and diabetes duration of 18.6 ± 8.5 years. In people with T2D, 48.2% (n = 665) were male, with a mean age of 60.5 ± 9.6 years and diabetes duration of 16.4 ± 9.8 years. Baseline characteristics in people with T1D or T2D stratified by being most active in the morning, or evening are provided in supplementary Table 1.

In people with T1D, M5time (linear) was not associated with HbA1c or lipid parameters across unadjusted and adjusted models after FDR correction. However, M5time (linear) showed a significant inverse association with waist circumference in model 3(B = −0.32, SE = 0.15, FDR p = 0.047) (Table 2). No other significant associations were observed in people with T1D.

When M5time was modelled using circular (sin/cos) terms, M5time (cos) was significantly associated with waist circumference across all models, including the unadjusted model (B = −4.15, SE = 1.28, FDR p = 0.002), model 2 (B = −4.10, SE = 1.18, FDR p = 0.001), and model 3 (B = −4.22, SE = 1.20, FDR p = 0.001). Similarly, M5time (cos) was significantly associated with BMI in all models, including the unadjusted model (B = −1.55, SE = 0.49, FDR p = 0.003), model 2 (B = −1.29, SE = 0.45, FDR p = 0.009), and Model 3 (B = −1.38, SE = 0.45, FDR p = 0.004) (Table 3). Wald tests confirmed these significant associations with joint p values for BMI 0.004 and Waist 0.001. No other associations were seen in people with T1D. Supplementary Table 1 presents the phase and amplitude data, alongside the outputs from the Wald test. BMI showed a significant rhythmic pattern, with an estimated amplitude of 1.32 $kg/m^2$ and a peak phase occurring at approximately 12:51 h (p = 0.004). Waist circumference also demonstrated a strong diurnal

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**Table 1** General Characteristics of People with Type 1 or Type 2 Diabetes Included in the Current Analysis

| | **Type 1 (n = 891)** | **Type 2 (n = 1381)** |
|---|---|---|
| | **Mean (SD) or n (%)** | **Mean (SD) or n (%)** |
| Sex = male (%) | 439 (49.3) | 665 (48.2) |
| Age (Years) | 34.4 (10.1) | 60.5 (9.6) |
| Diabetes duration (Years) | 18.6 (8.5) | 16.4 (9.8) |
| Height (cm) | 165.3 (9.6) | 164.6 (9.5) |
| Weight (kg) | 74.8 (15.6) | 84.2 (17.4) |
| BMI (Kg/m2) | 27.3 (4.8) | 31.1 (5.9) |
| Waist (cm) | 88.7 (13.8) | 103.7 (13.6) |
| Hba1c (mmol/mol) | 62.3 (14.8) | 58.2 (15.4) |
| Total cholesterol (mmol/mol) | 4.53 (0.99) | 4.01 (1.06) |
| HDL-cholesterol (mmol/mol) | 1.56 (0.44) | 1.33 (0.37) |
| LDL-cholesterol (mmol/mol) | 2.59 (0.93) | 2.04 (0.92) |
| Triglyceride (mmol/mol) | 0.93 (0.70) | 1.45 (0.99) |
| Medications | | |
| Glucose lowering | 170 (19.1) | 1320 (95.6) |
| Insulin | 891 (100.0) | 624 (45.2) |
| Lipid lowering | 514 (57.7) | 1153 (83.5) |
| Hypertension | 177 (19.9) | 639 (46.3) |
| GLP1_and SGLT2i | 334 (37.5) | 931 (67.4) |
| Comorbidities | | |
| CVD | 21 (2.4) | 243 (17.6) |
| CVA | 6 (0.7) | 33 (2.4) |
| Nephropathy | 57 (6.4) | 190 (13.8) |
| Retinopathy | 520 (58.4) | 780 (56.5) |
| Neuropathy | 162 (18.2) | 509 (36.9) |
| Dyslipidemia | 429 (48.1) | 1196 (86.6) |
| Hypertension | 161 (18.1) | 945 (68.4) |
| Smoking (yes) | 555 (62.3) | 1098 (79.5) |
| Ex- Smoker | 27 (3.0) | 77 (5.6) |
| Overall physical activity (mg) | 33.4 (10.3) | 28.0 (9.0) |
| M5value (mg) | 50.4 (17.6) | 41.8 (15.5) |
| M5time (hh:mm) | 14:46 | 13:00 |
| M5time (hh:mm) circular | 14:30 (2.83 h) | 12:57 (2.90 h) |

**Note**: M5 time is expressed in 24 h time.

**Table 2** Association of Accelerometer Measured M5 Time (linear) and M5 Value with the Outcomes of BMI, Waist Circumference and Lipid Profile in People with Type 1 Diabetes

| Outcome | Model 1 (Unadjusted) | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **M5 time (linear)** | **B(SE)** | **p.value** | **FDR (p-value)** | **B(SE)** | **p.value** | **FDR (p-value)** | **B(SE)** | **p.value** | **FDR (p-value)** |
| HbA1c | 0.29 (0.18) | 0.114 | 0.114 | 0.16 (0.18) | 0.374 | 0.467 | 0.22 (0.18) | 0.230 | 0.282 |
| Total cholesterol | −0.006 (0.01) | 0.626 | 0.626 | −0.004 (0.01) | 0.748 | 0.780 | −0.004 (0.01) | 0.767 | 0.776 |
| HDL cholesterol | 0.0001 (0.01) | 0.981 | 0.981 | 0.004 (0.01) | 0.537 | 0.672 | 0.003 (0.01) | 0.662 | 0.757 |
| LDL cholesterol | −0.012 (0.01) | 0.265 | 0.265 | −0.014 (0.01) | 0.206 | 0.344 | −0.014 (0.01) | 0.235 | 0.430 |
| BMI | −0.08 (0.06) | 0.164 | 0.164 | −0.10 (0.05) | 0.063 | 0.127 | −0.11 (0.05) | 0.035 | 0.065 |
| Waist circumference | −0.28 (0.16) | 0.069 | 0.069 | −0.30 (0.15) | 0.037 | 0.053 | −0.32 (0.15) | 0.030 | 0.047 |
| **M5value (mg)** | | | | | | | | | |
| HbA1c | −0.10 (0.03) | <0.001 | <0.001 | −0.10 (0.03) | <0.001 | 0.001 | −0.05 (0.11) | 0.670 | 0.758 |
| Total cholesterol | −0.003 (0.002) | 0.061 | 0.073 | −0.002 (0.002) | 0.402 | 0.510 | −0.011 (0.007) | 0.105 | 0.210 |
| HDL cholesterol | 0.002 (0.001) | 0.007 | 0.009 | 0.002 (0.001) | 0.003 | 0.007 | 0.002 (0.002) | 0.299 | 0.440 |
| LDL cholesterol | −0.005 (0.002) | 0.004 | 0.007 | −0.003 (0.002) | 0.068 | 0.124 | −0.014 (0.006) | 0.034 | 0.087 |
| BMI | 0.007 (0.008) | 0.400 | 0.436 | 0.02 (0.008) | 0.031 | 0.060 | −0.03 (0.02) | 0.166 | 0.275 |
| Waist circumference | −0.001 (0.02) | 0.949 | 0.949 | 0.002 (0.02) | 0.913 | 0.942 | −0.16 (0.07) | 0.016 | 0.052 |

**Notes**: Model 1 (Unadjusted); Model 2 (Adjusted): Model 1 + sex, age, duration of diabetes, smoking status, insulin therapy, other glucose-lowering medication, comorbidities, GLP-1/SGLT2 therapy, lipid-lowering therapy, and blood-pressure medication; Model 3 (Adjusted + PA): Model 2 + overall physical activity (accelerometer-derived mg).

**Table 3** Association of accelerometers measured M5 time (circular) with the outcomes of BMI, waist circumference and lipid profile in people with type 1 diabetes

| Type1 Diabetes | Circular (sin) M5time | | | Circular (cos) M5time | | | Wald Tests |
|---|---|---|---|---|---|---|---|
| **Model 1** | **B(SE)** | **p.value** | **FDR (p- value)** | **B(SE)** | **p.value** | **FDR (p- value)** | **Joint_p** |
| HbA1c | -0.65 (1.21) | 0.593 | 0.593 | 2.02 (1.59) | 0.206 | 0.309 | 0.110 |
| Total cholesterol | 0.001 (0.09) | 0.992 | 0.992 | -0.05 (0.10) | 0.611 | 0.916 | 0.816 |
| HDL cholesterol | 0.003 (0.05) | 0.953 | 0.953 | 0.007 (0.04) | 0.870 | 0.953 | 0.988 |
| LDL cholesterol | 0.04 (0.08) | 0.648 | 0.648 | -0.06 (0.10) | 0.563 | 0.648 | 0.480 |
| BMI | -0.54 (0.44) | 0.214 | 0.214 | -1.55 (0.49) | 0.002 | 0.003 | 0.005 |
| Waist circumference | -1.21 (1.06) | 0.256 | 0.256 | -4.15 (1.28) | 0.001 | 0.002 | 0.009 |
| **Model 2** | | | | | | | |
| HbA1c | -0.13 (1.26) | 0.921 | 0.921 | 1.72 (1.61) | 0.287 | 0.394 | 0.346 |
| Total cholesterol | -0.008 (0.09) | 0.933 | 0.933 | -0.05 (0.10) | 0.594 | 0.725 | 0.840 |
| HDL cholesterol | -0.007 (0.05) | 0.892 | 0.892 | 0.02 (0.04) | 0.542 | 0.745 | 0.697 |
| LDL cholesterol | 0.05 (0.09) | 0.545 | 0.609 | -0.06 (0.10) | 0.554 | 0.609 | 0.376 |
| BMI | -0.29 (0.41) | 0.477 | 0.657 | -1.29 (0.45) | 0.004 | 0.009 | 0.009 |
| Waist circumference | -1.21 (0.99) | 0.220 | 0.303 | -4.10 (1.18) | 0.001 | 0.001 | 0.002 |

(*Continued*)

**Table 3** (Continued).

| Type1 Diabetes | Circular (sin) M5time | | | Circular (cos) M5time | | | Wald Tests |
|---|---|---|---|---|---|---|---|
| **Model 1** | **B(SE)** | **p.value** | **FDR (p- value)** | **B(SE)** | **p.value** | **FDR (p- value)** | **Joint_p** |
| **Model 3** | | | | | | | |
| HbA1c | -0.16 (1.26) | 0.896 | 0.906 | 2.06 (1.59) | 0.195 | 0.263 | 0.210 |
| Total cholesterol | -0.008 (0.09) | 0.931 | 0.931 | -0.05 (0.10) | 0.608 | 0.811 | 0.851 |
| HDL cholesterol | -0.006 (0.05) | 0.905 | 0.905 | 0.02 (0.04) | 0.672 | 0.832 | 0.824 |
| LDL cholesterol | 0.05 (0.09) | 0.551 | 0.651 | -0.05 (0.10) | 0.597 | 0.651 | 0.419 |
| BMI | -0.28 (0.41) | 0.494 | 0.658 | -1.38 (0.45) | 0.002 | 0.004 | 0.004 |
| Waist circumference | -1.21 (1.00) | 0.225 | 0.300 | -4.22 (1.20) | <0.001 | 0.001 | 0.001 |

**Notes**: Model 1 (Unadjusted); Model 2 (Adjusted): Model 1 + sex, age, duration of diabetes, smoking status, insulin therapy, other glucose-lowering medication, comorbidities, GLP-1/SGLT2 therapy, lipid-lowering therapy, and blood-pressure medication; Model 3 (Adjusted + PA): Model 2 + overall physical activity (accelerometer-derived mg).

rhythm, with an amplitude of 4.28 cm and a peak phase at approximately 13:06 h (p = 0.001). No diurnal variation was observed in people T1D for HbA1c or lipid parameters.

When the exposure was the acceleration during this 5-hour period of peak physical activity (M5value), this was negatively associated with HbA1c in unadjusted model (B = −0.10, SE = 0.03, FDR p < 0.001) and in models 2 (B = −0.10, SE = 0.03, FDR p = 0.001), but this association no longer significant in model 3. Additionally, the M5value was positively associated with HDL cholesterol in unadjusted model (B = 0.002, SE = 0.001, FDR p = 0.009), and model 2 (B = 0.002, SE = 0.001, FDR p = 0.007), but not in model 3. Similarly, M5 values was negatively associated with LDL cholesterol in unadjusted models (B = −0.005, SE, 0.002, FDR p = 0.007), but not in model 2 and in model 3. No other significant associations were observed (Table 2). When stratifying the sample by morning or afternoon M5time, no differences were observed between both groups in T1D except for the start of the most active 5-hour period and the older age groups (supplementary Table 2).

In people with T2D, M5time (linear) was associated with total cholesterol in the unadjusted model (B = 0.21, SE = 0.01, FDR p = 0.036), but not in adjusted models. Similarly, linear M5time was associated with LDL cholesterol in unadjusted model (B = 0.23, SE = 0.009, FDR p = 0.009), but not in adjusted models (Table 4). No other associations with M5time (linear) were observed.

When M5time was modelled using circular (sin-cos) terms, M5time (sine) was associated in the unadjusted model with total cholesterol (B = −0.12, SE = 0.05, FDR p = 0.034), LDL cholesterol (B = −0.11, SE = 0.04, FDR p = 0.025) and BMI (B = −0.67, SE = 0.28, FDR p = 0.026), but these associations were lost after adjustment in model 2 and 3. In the unadjusted model, Wald tests demonstrated significant associations of M5time (circular) with LDL cholesterol (joint p = 0.021) and with BMI (joint p = 0.05), but not in models 2 or 3 (Table 5). No other associations were observed. Phase and amplitude data, with Wald tests, are presented in supplementary Table 1 with no associations observed.

The M5 value was negatively associated with HbA1c in the unadjusted model (B = −0.07, SE = 0.03, FDR p = 0.009) but not in the adjusted models. Additionally, M5 value was also associated with HDL cholesterol in the unadjusted model (B = 0.002, SE = 0.001, FDR p = 0.001) and adjusted model 2 (B = 0.003, SE = 0.001, FDR p < 0.001), but not in model 3. On top of this, M5 value was associated with BMI in unadjusted models (B = −0.06, SE = 0.01, FDR p < 0.001) and in model 2 (B = −0.06, SE = 0.01, FDR p < 0.001). Similar results for waist circumference in the unadjusted model (B = −0.15, SE = 0.02, FDR p < 0.001) and in models 2 (B = −0.15, SE = 0.02, FDR p < 0.001), although this did not remain significant in model 3. No other significant associations were observed (Table 4). When stratifying by morning or afternoon M5time, differences were observed between both groups in T2D for total cholesterol, LDL-cholesterol, the start of the most active 5-hour period and the age (supplementary Table 2).

**Table 4** Association of Accelerometer Measured M5 Time (linear) and M5 Value with the Outcomes of BMI, Waist Circumference and Lipid Profile in People with Type 2 Diabetes

| Outcomes | Model 1 (Unadjusted) | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **M5 time (linear)** | **B (SE)** | **p.value** | **FDR (p-value)** | **B (SE)** | **p.value** | **FDR (p-value)** | **B (SE)** | **p.value** | **FDR (p-value)** |
| HbA1c | 0.29 (0.15) | 0.052 | 0.052 | 0.21 (0.14) | 0.148 | 0.272 | 0.20 (0.14) | 0.173 | 0.297 |
| Total cholesterol | 0.021 (0.010) | 0.036 | 0.036 | 0.007 (0.010) | 0.492 | 0.601 | 0.007 (0.010) | 0.468 | 0.562 |
| HDL cholesterol | −0.004 (0.003) | 0.204 | 0.204 | −0.005 (0.003) | 0.154 | 0.190 | −0.004 (0.003) | 0.215 | 0.285 |
| LDL cholesterol | 0.023 (0.009) | 0.009 | 0.009 | 0.01 (0.009) | 0.255 | 0.393 | 0.01 (0.009) | 0.249 | 0.427 |
| BMI | 0.09 (0.05) | 0.112 | 0.112 | 0.029 (0.056) | 0.600 | 0.600 | 0.014 (0.054) | 0.790 | 0.790 |
| Waist circumference | 0.053 (0.124) | 0.672 | 0.672 | 0.050 (0.128) | 0.694 | 0.764 | 0.013 (0.125) | 0.916 | 0.916 |
| **M5value (mg)** | | | | | | | | | |
| HbA1c | −0.07 (0.03) | 0.008 | 0.009 | −0.05 (0.03) | 0.063 | 0.126 | 0.03 (0.13) | 0.836 | 0.952 |
| Total cholesterol | 0.003 (0.002) | 0.114 | 0.114 | 0.002 (0.002) | 0.274 | 0.403 | 0.0004 (0.007) | 0.958 | 0.982 |
| HDL cholesterol | 0.002 (0.001) | 0.001 | 0.001 | 0.003 (0.001) | <0.001 | <0.001 | −0.0004 (0.003) | 0.884 | 0.952 |
| LDL cholesterol | 0.003 (0.002) | 0.082 | 0.089 | 0.0005 (0.001) | 0.736 | 0.847 | 0.001 (0.006) | 0.864 | 0.952 |
| BMI | −0.06 (0.01) | <0.001 | <0.001 | −0.06 (0.01) | <0.001 | <0.001 | 0.004 (0.04) | 0.928 | 0.975 |
| Waist circumference | −0.15 (0.02) | <0.001 | <0.001 | −0.15 (0.02) | <0.001 | <0.001 | 0.12 (0.10) | 0.261 | 0.534 |

**Notes**: Model 1 (Unadjusted); Model 2 (Adjusted): Model 1 + sex, age, duration of diabetes, smoking status, insulin therapy, other glucose-lowering medication, comorbidities, GLP-1/SGLT2 therapy, lipid-lowering therapy, and blood-pressure medication; Model 3 (Adjusted + PA): Model 2 + overall physical activity (accelerometer-derived mg).

**Table 5** Association of accelerometers measured M5 time (circular) with the outcomes of BMI, waist circumference and lipid profile in people with type 2 diabetes

| Type 2 Diabetes | Circular (sin) M5time | | | Circular (cos) M5time | | | Wald Tests |
|---|---|---|---|---|---|---|---|
| **Model 1** | **B(SE)** | **p.value** | **FDR (p- value)** | **b (se)** | **p.value** | **FDR (p- value)** | **Joint_p** |
| HbA1c | -1.56 (0.74) | 0.036 | 0.054 | -0.44 (1.45) | 0.761 | 0.761 | 0.118 |
| Total cholesterol | -0.12 (0.05) | 0.023 | 0.034 | -0.04 (0.09) | 0.677 | 0.677 | 0.074 |
| HDL cholesterol | 0.009 (0.018) | 0.634 | 0.634 | -0.04 (0.03) | 0.182 | 0.272 | 0.270 |
| LDL cholesterol | -0.11 (0.04) | 0.016 | 0.025 | 0.05 (0.08) | 0.516 | 0.516 | 0.021 |
| BMI | -0.67 (0.28) | 0.018 | 0.026 | -0.72 (0.48) | 0.138 | 0.138 | 0.050 |
| Waist circumference | -0.42 (0.64) | 0.506 | 0.758 | -0.16 (1.18) | 0.893 | 0.893 | 0.818 |
| **Model 2** | | | | | | | |
| HbA1c | -1.11 (0.75) | 0.139 | 0.279 | 0.14 (1.37) | 0.916 | 0.916 | 0.274 |
| Total cholesterol | -0.04 (0.05) | 0.480 | 0.640 | -0.01 (0.09) | 0.886 | 0.966 | 0.775 |
| HDL cholesterol | 0.02 (0.02) | 0.281 | 0.338 | -0.01 (0.03) | 0.745 | 0.745 | 0.438 |
| LDL cholesterol | -0.04 (0.04) | 0.334 | 0.502 | 0.04 (0.08) | 0.644 | 0.702 | 0.450 |
| BMI | -0.38 (0.29) | 0.186 | 0.223 | -0.62 (0.50) | 0.209 | 0.228 | 0.277 |
| Waist circumference | -0.48 (0.65) | 0.461 | 0.554 | -0.17 (1.20) | 0.887 | 0.919 | 0.773 |

(*Continued*)


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**Table 5** (Continued).

| Type 2 Diabetes | Circular (sin) M5time | | | Circular (cos) M5time | | | Wald Tests |
|---|---|---|---|---|---|---|---|
| **Model 1** | **B(SE)** | **p.value** | **FDR (p- value)** | **b (se)** | **p.value** | **FDR (p- value)** | **Joint_p** |
| **Model 3** | | | | | | | |
| HbA1c | -1.05 (0.75) | 0.161 | 0.299 | 0.09 (1.35) | 0.950 | 0.950 | 0.318 |
| Total cholesterol | -0.04 (0.05) | 0.460 | 0.598 | -0.01 (0.09) | 0.901 | 0.976 | 0.756 |
| HDL cholesterol | 0.02 (0.02) | 0.353 | 0.417 | -0.007 (0.03) | 0.824 | 0.855 | 0.565 |
| LDL cholesterol | -0.04 (0.05) | 0.327 | 0.532 | 0.04 (0.08) | 0.638 | 0.691 | 0.438 |
| BMI | -0.32 (0.28) | 0.257 | 0.278 | -0.69 (0.49) | 0.157 | 0.185 | 0.278 |
| Waist circumference | -0.32 (0.64) | 0.613 | 0.763 | -0.35 (1.17) | 0.763 | 0.763 | 0.873 |

**Notes**: Model 1 (Unadjusted); Model 2 (Adjusted): Model 1 + sex, age, duration of diabetes, smoking status, insulin therapy, other glucose-lowering medication, comorbidities, GLP-1/SGLT2 therapy, lipid-lowering therapy, and blood-pressure medication; Model 3 (Adjusted + PA): Model 2 + overall physical activity (accelerometer-derived mg).

## Discussion

This current study provides novel findings on the association between the time of day the most active 5 hours occur with cardiometabolic markers. By combining linear, intensity-based, and circular (sin–cos) modelling approaches, this study provides a comprehensive evaluation of whether when and how intensely people are most active is associated with cardiometabolic health, independent of total physical activity volume.

In people with T1D, linear modelling approaches demonstrated a significant association of the most active 5 hours with waist circumference, and circular models further demonstrated strong associations with both BMI and waist circumference that persisted even after full adjustment, including for overall physical activity. Additionally, joint Wald tests from fully adjusted models showed significant circadian associations for BMI (amplitude 1.32 $kg/m^2$; phase 12:51h; joint $p = 0.004$) and waist circumference (amplitude 4.28 cm; phase 13:06h; joint $p = 0.001$), indicating that peak activity occurring around the early afternoon was associated with more favourable body composition in T1D, independent of overall physical activity volume. In contrast, no significant associations were observed between the time of day of most active 5 hours with HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol in people with T1D. This lack of association was consistent across linear, intensity-based, and circular models, with joint Wald tests confirming no significant rhythmic effects for glycemic or lipid outcomes. Together, these results indicate that while the timing of peak physical activity may be modestly relevant for body composition in T1D, it appears to have limited influence on glycemic control or lipid profiles.

This contrasts, the current data demonstrated that the amount of physical activity in the most active 5 hours was negatively associated with HbA1c and HDL cholesterol, after adjustment for demographic and clinical covariates. However, these associations were no longer statistically significant after further adjustment for overall physical activity, which is perhaps not surprising as these are closely related. This suggests that total physical activity volume accumulated across the day, rather than the physical activity during the most active 5 hours, is the primary driver of these metabolic associations in T1D.

In people with T2D, both linear and circular modelling approaches demonstrated that the time of day of most active 5 hours was not associated with any variables in adjusted models. These results indicating that activity timing does not exert a strong independent circadian influence on cardiometabolic health in T2D. In contrast, the amount of physical activity in the most active 5 hours was associated with waist circumference, BMI and HDL cholesterol, although these associations were attenuated after adjustment for overall physical activity. This highlights, as in people with T1D, the dominant role of total activity volume over the peak activity intensity or timing.

Overall, these findings indicate that total physical activity volume remains the most important determinant of favourable cardiometabolic health outcomes in both T1D and T2D, whereas the timing of peak physical activity appears to have a more limited and condition-specific role. For public health prospective, strategies should focus on promotion of

physical activity at any time of day in people with diabetes, although there may be a small further benefit in people with T2D to perform physical activity earlier in the day.

This is the first study to objectively measure physical activity and individuals most active time of day and how this is associated with cardiometabolic health outcomes in people with T1D and T2D. Prior to this study, few studies explored the timing of physical activity and its association with health indices in people with diabetes. For example, analysis of the look AHEAD trial reported that, in people with type 2 diabetes, physical activity performed in afternoon was associated with the greatest HbA1c reduction, at one year, in response to the dietary and physical activity weight loss intervention. This reduction was 30–50%, or approximately a 0.1% unit HbA1c difference, greater than when physical activity was performed at different times of day.[23] Analysis from the same study reported that physical activity in the morning time was associated with the highest CVD risk score among males with T2D.[32] In another study, in a retrospective analysis of an exercise intervention in people at risk of or with T2D, reported that after 12 weeks of exercise training those who exercised in the afternoon had a greater increase in skeletal muscle insulin sensitivity, adipose tissue lipolysis and reduction of fat mass than those exercise training in morning.[24] There are very few randomised control trials which have investigated the effect of time of day on metabolic responses to exercise. Most of these studies indicated the afternoon exercise is more efficacious than the morning exercise.[22,24,27] However, all these studies have small sample sizes and mainly focused on the short-term effects of structured exercise timing on metabolic functions. For example, a study reported that, in people with T2D, two weeks of afternoon high-intensity training was more efficacious than morning training in lowering blood glucose levels in T2D.[22] However, no differences in HDL-C or LDL-C levels were found comparing morning versus afternoon exercise.[22] In people with type 1 diabetes, a single session of resistance exercise, in a fasting condition, in the morning resulted in an increase in blood glucose, while afternoon exercise resulted in decrease of blood glucose levels in T1D.[27] However, the present findings suggest that these benefits are primarily driven by how much activity is performed rather than when it occurs. Nevertheless, the observed circadian associations with adiposity in T1D suggest that activity timing may modestly interact with behavioural or physiological rhythms relevant to energy balance in this population.

The majority of the above findings are in contrast to the current study where we found very little effect of the time of day of the most active 5 hours on cardiometabolic health outcomes in both people with T1D and T2D. The current data is, however, supported by a large cohort study which provides evidence that moderate to vigorous level of physical activity lower the risk of CVD regardless of the time of day.[20] In our analysis, we did, however, find no association between time of day of most active 5 hours and HbA1c in both people with T1D and T2D, that is in contrast to the aforementioned work showing greater benefits of afternoon exercise.

The differential findings in people with T1D and T2D may reflect fundamental differences in disease pathophysiology, treatment approaches, and lifestyle patterns. In people with T2D, insulin resistance and features of metabolic syndrome are more prominent, and physical activity plays a central role in enhancing insulin sensitivity, improving glucose uptake, and modulating lipid metabolism.[12] As a result, the timing of physical activity may have a more pronounced impact on cardiometabolic outcomes in T2D. In contrast, people with T1D are dependent on exogenous insulin, and their glycemic variability is more influenced by insulin dosing strategies, carbohydrate intake, and individual behavioral factors.[33] These factors may attenuate or obscure the potential impact of activity timing in this population. This requires to be investigated in more depth in further research.

The present findings may contribute to enhancing adherence to physical activity recommendations among individuals with diabetes. Adherence is influenced by multiple interrelated factors, including perceived benefits, motivation, social support, and access to suitable environments for physical activity.[34] By providing further detailed information on potential benefits at different times of day, this can empower individuals in their adherence to physical activity.

## Strengths and Limitations

The reasons for the differences between our study and previous work likely relate to the study design. In the current study, we have chosen to investigate the associations of time of day being most active with cardiometabolic outcomes in a reasonable large cohort of people with T1D or T2D, which is both a strength and a limitation of the study. This is a more pragmatic analysis than much of the previous work and it allows us to see, under real life conditions, whether the

time of day people are most active and at levels of normal physical activity is associated with any cardiometabolic health outcomes. Such data is crucial in developing realistic public health strategies. On top of this, the current study fully control or measure potential confounding variables, such as dietary intake or medications, as is seen during randomised controlled trials, and this limits our ability to infer causality. Building on this, the current study is a cross-sectional analysis, where physical activity, HbA1c, body composition and lipid profile were measured or collected at the same time; however, as the study is not interventional or longitudinal we cannot confirm causality in the relationships observed. Moreover, the participants in this study were all Kuwaiti and living in Kuwait and this geographic and ethnic specificity may partially limit the generalizability of the findings.

## Conclusion

In conclusion, our data indicate very little association of time of day of the most active 5 hours with the cardiometabolic health outcomes assessed. In people with T1D, BMI and waist circumference showed significant daily rhythmic patterns with peaks around midday, while no diurnal variation was observed for glycaemic control or lipid parameters. In contrast, no cardiometabolic outcomes showed significant diurnal rhythmicity in their association with physical activity in people with T2D after full adjustment. In conclusion, therefore, public health strategies should focus on increasing physical activity at a time of day preferred, convenient and sustainable for the individual with diabetes.

## Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethical Approval and Consent to Participate

The study was approved by the Dasman Diabetes Institute Ethical Review Committee, Kuwait (RA HM- 2020- 018) and followed the guidelines set out in the Declaration of Helsinki. All participants signed the consents and agreed to follow.

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## Author Contributions

EAO, MI, SGR: Conceptualization; methodology, data curation, formal analysis, validation, visualization, writing – original draft, writing – review and editing. JA, AAO, DA, DS: Data curation, writing – review and editing. NS, BVS: methodology, validation, writing – review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Each author declares that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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