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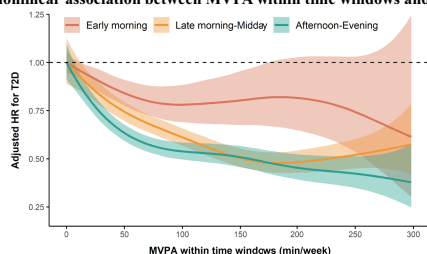
Associations of Moderate-to-Vigorous Physical Activity Timing With Type 2 Diabetes Incidence in UK Biobank and Prevalent Glycemic Measures in NHANES

Study Population: Participants with acceleration data **Exposure:** Timing of MVPA **Outcome:** Diabetes and Glycemic measures



UK Biobank—Prospective Outcome: Type 2 diabetes (T2D) incidence

The nonlinear association between MVPA within time windows and T2D risk



Early morning
0500–959



Late morning-midday
1000–1459



Afternoon-evening
1500–2400

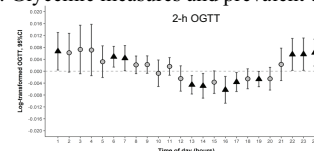
The association between the timing of MVPA (categorical) and T2D risk

Early morning MVPA	Reference
Late morning-midday MVPA	HR = 0.80 (0.68, 0.95)
Afternoon-evening MVPA	HR = 0.71 (0.59, 0.85)
Variable-timing MVPA	HR = 0.75 (0.62, 0.91)



U.S. National Health and Nutrition Examination Surveys — Cross-sectional Outcome: Glycemic measures and prevalent diabetes

Afternoon and early evening MVPA were associated with favorable glycemic measures (most pronounced in result of 2-h OGTT) and lower diabetes prevalence.



Conclusion When keeping total MVPA volume constant, clustering MVPA in the afternoon-evening was associated with the strongest reduction in incident T2D risk, fewer prevalent diabetes and more favorable glycemic measure.

HR, hazard ratio; MVPA, moderate-to-vigorous physical activity; NHANES, National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test.

ARTICLE HIGHLIGHTS

- Why did we undertake this study?**
 While the benefit of engaging in moderate-to-vigorous physical activity (MVPA) for diabetes prevention is well established, the independent role of MVPA timing during the day remains underexplored.
- What is the specific question we wanted to answer?**
 We investigated whether MVPA timing was associated with type 2 diabetes risk and glycemic measures.
- What did we find?**
 The results showed that while keeping total MVPA constant, MVPA clustered in the afternoon-evening was associated with the lowest risk of incident type 2 diabetes, fewer prevalent diabetes, and more favorable glycemic measures.
- What are the implications of our findings?**
 The timing of MVPA may be a novel strategy for improved type 2 diabetes prevention.



Associations of Moderate-to-Vigorous Physical Activity Timing With Type 2 Diabetes Incidence in UK Biobank and Prevalent Glycemic Measures in NHANES

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OBJECTIVE

We assessed the association between timing of moderate-to-vigorous physical activity (MVPA) with incident type 2 diabetes (T2D) and glycemic measures.

RESEARCH DESIGN AND METHODS

Regression models were used to assess associations between accelerometer-derived MVPA timing and incident T2D in UK Biobank (UKB) ($n = 84,528$, prospective), prevalent diabetes, and glycemic measures in the National Health and Nutrition Examination Survey (NHANES) ($n = 6,998$, cross-sectional).

RESULTS

In UKB, with early morning (0500–0959) MVPA as reference and before adjustment for total MVPA, “variable-timing” MVPA was associated with the lowest incident T2D risk; while after adjustment, afternoon-evening MVPA (1500–2400) showed the lowest incident T2D risk. In NHANES, afternoon/early evening MVPA was weakly associated with more favorable glycemic measures and lower diabetes prevalence after adjustment for total MVPA.

CONCLUSIONS

When keeping total MVPA volume constant, clustering MVPA in the afternoon-evening was associated with the strongest reduction in incident T2D risk, fewer prevalent diabetes, and more favorable glycemic measures.

In addition to the generally accepted health benefits of physical activity amount, accumulating evidence has shown associations between physical activity timing and cardiometabolic disease outcomes, such as obesity (1,2), cardiovascular disease (3–5), type 2 diabetes (T2D) (6–8), and glycemic measures (9–13). Our previous studies in the National Health and Nutrition Examination Survey (NHANES) (7) and UK Biobank (UKB) (8) showed that timing of overall physical activity was associated with diabetes risk and glycemic measures. However, overall activity largely reflects fixed routines (e.g., work or household tasks) and is less modifiable. In contrast, moderate-to-vigorous physical activity (MVPA)—primarily representing exercise—is discretionary and more flexibly timed, making it more applicable to exercise recommendations. Some studies observed that MVPA/exercise timing associated with glucose metabolism (11–15), with most (11,13–15) finding greater benefits when

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performed in the afternoon or evening rather than in the morning. However, these studies were generally performed in small samples, and none of them investigated the association between MVPA timing and T2D risk.

We hypothesized that afternoon and evening MVPA has the largest metabolic benefits for diabetes prevention. Here, we examined the associations between MVPA timing and T2D risk in UKB, independent of the total MVPA volume. To provide supportive evidence from prevalent diabetes and glycemic measures, we additionally used cross-sectional data from NHANES.

RESEARCH DESIGN AND METHODS

The current study was performed using available data from the UKB and NHANES. In UKB, time-to-event analyses were performed on T2D embedded in the accelerometer substudy (Supplementary Fig. 1). In NHANES, cross-sectional analyses were performed on prevalent diabetes and glycemic measures (fasting glucose, fasting insulin, HOMA insulin resistance [HOMA-IR], and oral glucose tolerance test [OGTT]) among participants with actigraphy data in the NHANES 2011–2014 cycles (Supplementary Fig. 2). Hourly MVPA was used as exposure in both UKB and NHANES. Associations between hourly MVPA minutes with T2D incidence in UKB and prevalent diabetes and glycemic measures in NHANES were examined using Cox proportional hazard and logistic/linear regression models, respectively. Additionally, in UKB, nonnocturnal hours (0500–2359) were divided into three time windows using a data-driven approach (see Supplementary Methods). Nonlinear associations between MVPA in each time window and T2D risk were modeled using penalized cubic splines. Participants were assigned to different timing groups according to the time of day when their >50% MVPA occurred, and T2D risk across different MVPA timing groups was compared. As sensitivity analyses, the same analyses have been conducted using a non-data-driven

approach and sleep-referenced timing windows. Extensive descriptions of methodology are described in the Supplementary Methods.

RESULTS

UKB

Table 1 shows characteristics of the 84,528 UKB participants. Over a median of 7.5 years (638,035 person-years) follow-up, T2D developed in 2,015 participants (2.4%). Participants in the “variable-timing” group had the highest mean total MVPA volume.

As shown in Fig. 1A, increasingly later MVPA during daytime hours was associated with increasingly lower T2D risk in model 1. After adjusting for total MVPA in model 2, only MVPA during 1900–1959 (hazard ratio [HR] 0.96, 95% CI 0.94–0.99) was associated with lower T2D risk (Supplementary Table 4). Figure 1B shows the nonlinear association between MVPA in three time windows with T2D risk, adjusting for all covariates in model 1, plus MVPA during the other two time windows. In general, higher MVPA within any of the three time windows was associated with lower T2D risk; however, MVPA performed during the two time windows—late morning-midday and afternoon-evening—was associated with a stronger reduction in T2D risk than MVPA in the early morning. In the substitution model, reallocating 20% substitution of MVPA from the early morning to the afternoon-evening was associated with a 9% lower risk of T2D (HR 0.91, 95% CI 0.86–0.95).

In Table 2, compared with the early morning group, the late morning-midday, afternoon-evening, and variable-timing groups all showed lower risks for incident T2D before and after adjusting for total MVPA (models 2 and 3). The variable-timing group showed the lowest risk before adjusting for total MVPA (model 2), while we observed the largest reduction in incident T2D risk in the afternoon-evening group after adjusting for total MVPA (model 3). After additional adjustment for shift work and for BMI or waist circumference (the latter as potential mediators), the lower T2D risk associated

with afternoon-evening MVPA persisted, although the effect size attenuated after adjusting for adiposity measures (data not shown). In contrast, the association for the late morning-midday MVPA and variable-timing MVPA and incident T2D disappeared (data not shown). Sensitivity analyses using a non-data-driven approach and sleep-referenced time windows showed similar results (Supplementary Table 5).

NHANES

Participant characteristics are summarized in Supplementary Table 3. We observed (Fig. 2A) a trend for a lower likelihood of prevalent diabetes related to afternoon MVPA. While most associations were small to negligible, we observed a lower odd of diabetes with MVPA during 1700–1759 (odds ratio 0.96, 95% CI 0.93–1.00, $P = 0.034$). In addition, a weaker but comparable trend to the lower diabetes prevalence in individuals with afternoon-early evening MVPA was observed for associations of MVPA timing with glycemic measures (plasma glucose after the 2-h OGTT) (Fig. 2B), HOMA-IR (Fig. 2C), fasting glucose (Supplementary Fig. 3A), and fasting insulin (Supplementary Fig. 3B).

CONCLUSIONS

In UKB participants, afternoon-evening MVPA was associated with lower risk of incident T2D compared with early morning MVPA. We observed similar trends in NHANES data, with MVPA during afternoon and early evening being weakly associated with lower diabetes prevalence and more favorable glycemic measures.

Our observation of the association of late afternoon/early evening MVPA with a lower risk of T2D partly differed from our previous studies (7,8) on overall physical activity timing, where both late morning and late afternoon activity were observed as optimal. This discrepancy likely reflects the distinction between overall physical activity timing, which captures daily habitual work and life

Table 1—Baseline characteristics in UKB participants having accelerometry data and without preexisting diabetes

Characteristic	Overall (N = 84,528)	Early morning MPVA (n = 4,469)	Late morning-midday MPVA (n = 40,312)	Afternoon-evening MPVA (n = 23,489)	Variable timing MVPA (n = 16,258)
Age, years	63 (56, 68)	63 (55, 68)	65 (59, 69)	60 (53, 66)	60 (53, 66)
Female sex	48,056 (57)	2,541 (57)	23,069 (57)	13,879 (59)	8,567 (53)
BMI, kg/m ²	25.9 (23.5, 28.8)	26.6 (23.9, 29.7)	26.0 (23.6, 28.8)	25.8 (23.4, 28.8)	25.5 (23.2, 28.2)
European ethnicity	82,062 (97)	4,303 (96)	39,454 (98)	22,584 (96)	15,721 (97)
Townsend deprivation index	−2.48 (−3.83, −0.25)	−2.50 (−3.82, −0.40)	−2.64 (−3.92, −0.62)	−2.36 (−3.77, 0.03)	−2.22 (−3.69, 0.25)
Education					
Degree or above	37,347 (44)	1,662 (37)	16,333 (41)	11,195 (48)	8,157 (50)
Any other qualification	40,546 (48)	2,321 (52)	20,027 (50)	11,021 (47)	7,177 (44)
No qualification	6,635 (7.8)	486 (11)	3,952 (9.8)	1,273 (5.4)	924 (5.7)
Smoking status					
Never	48,891 (58)	2,393 (54)	22,845 (57)	13,888 (59)	9,765 (60)
Previous	30,024 (36)	1,773 (40)	14,903 (37)	7,868 (33)	5,480 (34)
Current	5,613 (6.6)	303 (6.8)	2,564 (6.4)	1,733 (7.4)	1,013 (6.2)
Alcohol intake frequency					
≥3 times per week	42,059 (52)	2,041 (49)	20,258 (53)	11,531 (52)	8,229 (53)
<3 times per week	37,978 (47)	2,124 (51)	17,909 (47)	10,719 (48)	7,226 (47)
Never	294 (0.4)	16 (0.4)	148 (0.4)	81 (0.4)	49 (0.3)
Sleep midpoint	0302 (0230, 0334)	0238 (0204, 0310)	0304 (0231, 0336)	0311 (0238, 0344)	0252 (0222, 0321)
Sleep duration, h	7.33 (6.76, 7.86)	7.25 (6.66, 7.79)	7.44 (6.87, 7.96)	7.25 (6.68, 7.78)	7.24 (6.68, 7.74)
Season wearing accelerometer					
Spring	19,210 (23)	960 (21)	8,771 (22)	5,540 (24)	3,393 (24)
Summer	22,116 (26)	1,102 (25)	9,634 (24)	6,959 (30)	4,421 (27)
Autumn	25,166 (30)	1,324 (30)	12,335 (31)	6,788 (29)	4,719 (29)
Winter	18,036 (21)	1,083 (24)	9,572 (24)	4,202 (18)	3,179 (20)
Diabetes family history	13,417 (16)	745 (17)	6,241 (15)	3,837 (16)	2,594 (16)
Osteoporosis	2,476 (2.9)	120 (2.7)	1,387 (3.4)	626 (2.7)	343 (2.1)
Self-reported diet (weekly)					
Vegetable intake (tablespoon)	28.0 (21.0, 42.0)	28.0 (21.0, 42.0)	28.0 (21.0, 42.0)	28.0 (21.0, 42.0)	28.0 (21.0, 42.0)
Fruit intake (serving)	15.4 (8.4, 22.4)	15.4 (8.4, 22.4)	15.4 (8.4, 22.4)	14.0 (8.4, 22.4)	15.4 (8.4, 22.4)
Processed meat frequency (2–4 times)	21,216 (25)	1,148 (26)	10,062 (25)	5,889 (25)	4,117 (25)
Red meat frequency (2–4 times)	37,276 (44)	2,006 (45)	18,340 (45)	9,977 (42)	6,953 (43)
Sugar sweetened foods/drinks (never)	11,696 (14)	732 (16)	6,054 (15)	2,846 (12)	2,064 (13)
MVPA min/week	240 (122, 407)	209 (92, 361)	223 (109, 391)	209 (101, 357)	340 (206, 525)

Data are presented as median (interquartile range) or *n* (%). MVPA timing: early morning (0500–0959), late morning-midday (1000–1459), afternoon-evening (1500–2400).

routines, and MVPA timing, which more reflects intentional exercise. Given that MVPA may exert more beneficial effects on metabolic health and its timing is more amenable to behavioral modification than overall physical activity, we consider MVPA timing to be more relevant for exercise recommendations. Interestingly, we found that the variable-timing group had the highest mean total MVPA volume and showed the greatest risk reduction before adjustment for total MVPA. This suggests that distributing

MVPA across the day may result in higher MVPA accumulation and represents a pragmatic, effective strategy for T2D prevention. However, when total MVPA volume is constant, MVPA performed during evening may be most optimal.

In NHANES, the observed trends reflecting better glycemic measures with late afternoon/evening MVPA were consistent with earlier studies (11,14–16). Two prior studies observed that later-day activity and afternoon MVPA gave stronger

HbA_{1c} reduction (15,16). Others observed associations between afternoon/evening MVPA with better glucose homeostasis (14) and lower insulin resistance (11). Concordantly, some intervention studies found benefits of afternoon or evening MVPA/exercise on glycemic measures. For example, two small crossover trials (*n* = 52 and *n* = 11) observed evening exercise was more effective than morning exercise at suppressing nocturnal blood glucose rises (10) and reducing blood glucose concentration (13). However,

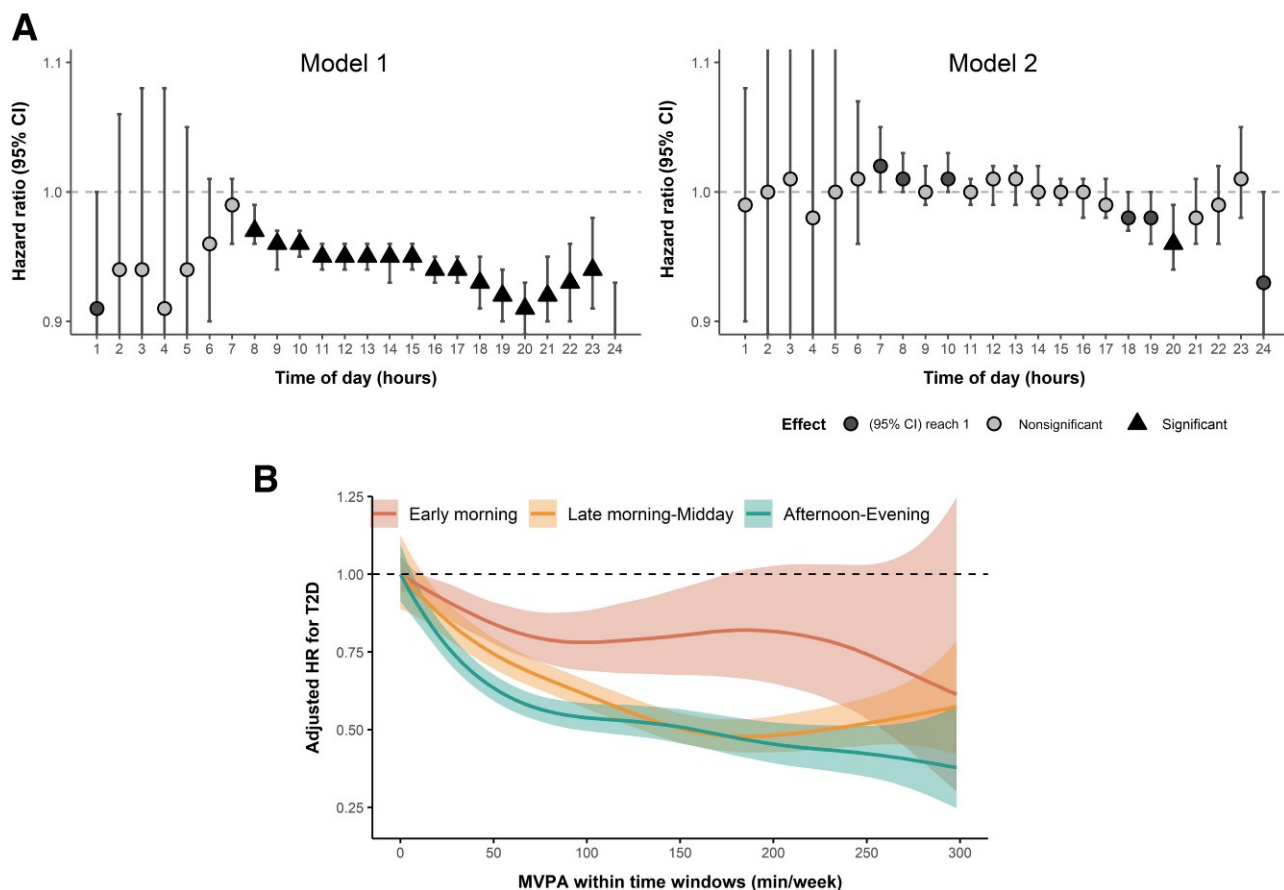


Figure 1—A: Associations between MVPA minutes during each hour of the day and T2D risk presented as HRs (95% CI) in UKB, model 1 adjusting for age, sex, ethnicity, Townsend deprivation index, education, smoking status, alcohol intake frequency, sleep midpoint, dietary information, sleep duration, season of accelerometry wear, and family history of diabetes. Model 2 additionally adjusted for total daily MVPA. **B:** Multivariable-adjusted associations between duration of MVPA within three time windows and T2D risk in UKB. For each time window, the reference value is 0 min of MVPA within that window. The HRs were adjusted for age, sex, ethnicity, Townsend deprivation index, education, smoking status, alcohol intake frequency, sleep midpoint, dietary information, sleep duration, season of accelerometry wear, and familial history of diabetes and MVPA volume during other two time windows.

another small trial ($n = 40$) found no significant differences in glycemic measures between morning and evening exercise (12). Nevertheless, the consistency across multiple observational and intervention studies supports the plausibility of our findings. Collectively, these observations suggest that MVPA in afternoon/evening may confer greater benefits for glucose regulation and T2D prevention.

The potential underlying mechanisms may relate to the circadian rhythm of insulin sensitivity. In humans, insulin sensitivity declines as the day progresses, with a significant reduction in the evening (17), leading to greater postprandial glucose responses of the evening meal (18). Engaging in MVPA in the late afternoon/evening might counteract this circadian decline by enhancing glucose uptake (19)

to help suppress higher glucose increase of the evening meal (20). Thus, aligning exercise with the biological window of reduced insulin sensitivity could help stabilize overall glucose balance and therefore lower diabetes risk. Nonetheless, the exact mechanisms remain to be clarified.

The strengths of this study include the large sample size, the use of accelerometry-measured MVPA, and various

Table 2—Differences in T2D risk between different MVPA timing groups in UKB

Group	Events/ <i>n</i>	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
MVPA				
Early morning	158/4,469	1.00 (reference)	1.00 (reference)	1.00 (reference)
Late morning-midday	1,058/40,312	0.70 (0.59, 0.83)	0.76 (0.64, 0.90)	0.80 (0.68, 0.95)
Afternoon-evening	502/23,489	0.67 (0.56, 0.80)	0.72 (0.60, 0.87)	0.71 (0.59, 0.85)
Variable timing	297/16,258	0.55 (0.45, 0.66)	0.60 (0.50, 0.73)	0.75 (0.62, 0.91)

Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for ethnicity, Townsend Deprivation Index, education, smoking status, alcohol intake frequency, sleep midpoint, dietary information, sleep duration, season of accelerometry wear, family history of diabetes, and osteoporosis. Model 3 was further adjusted for total daily MVPA.

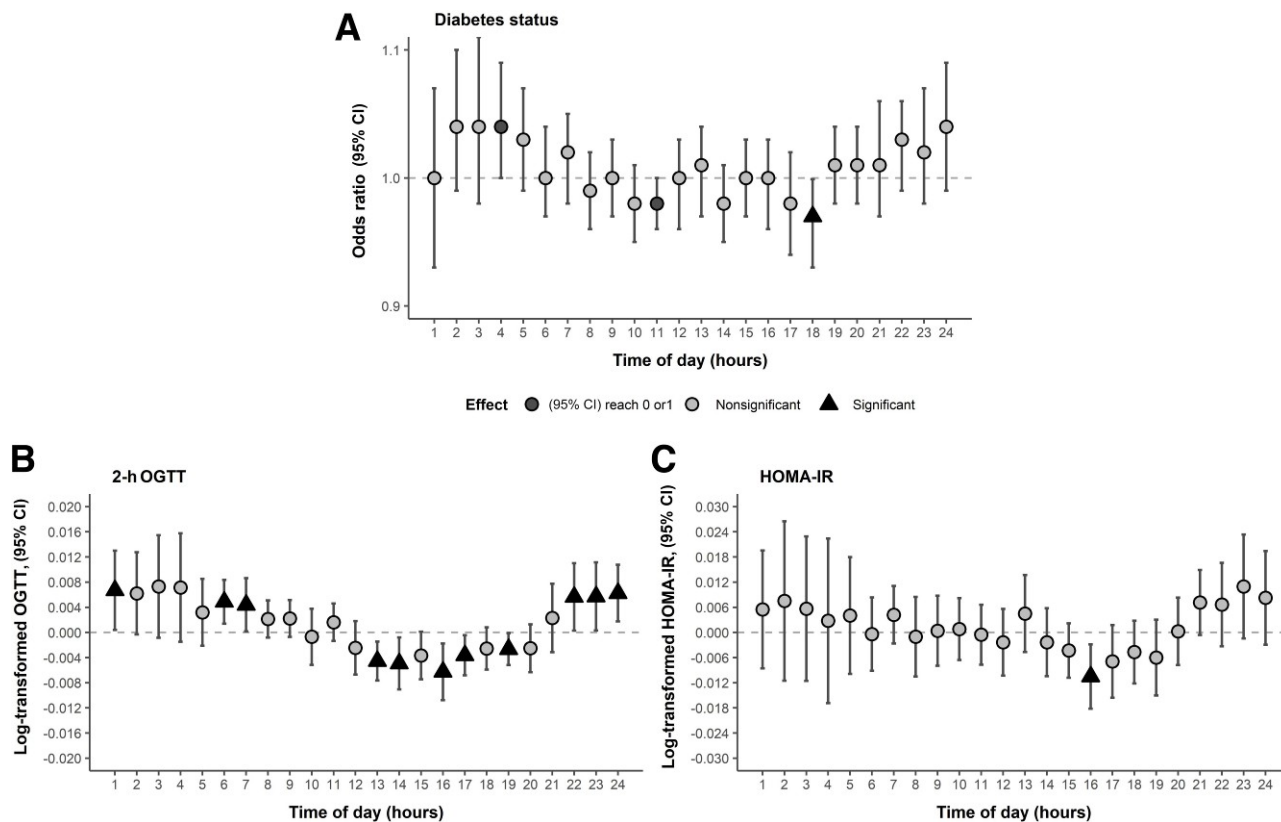


Figure 2—Multivariable-adjusted associations between MVPA minutes during each hour of the day and prevalent diabetes (A), 2-h OGTT results (B), and HOMA-IR (C) among NHANES (2011–2014) participants. Multiple logistic/linear regression models adjusted for age and sex, ethnicity, education, household income, marital status, smoking status, alcohol consumption, total energy intake, Healthy Eating Index (HEI) score, arthritis, sleep duration, sleep midpoint, and total daily MVPA.

outcomes. However, several limitations remain. First, some covariates in UKB were measured years before accelerometer data collection, potentially introducing bias from subsequent changes. BMI might be a mediator between MVPA timing and T2D risk; however, formally evaluating mediation with BMI measured years before the exposure assessment is not possible. Therefore, we included BMI in an additional sensitivity model. Second, the early morning (0500–0959) MVPA group comprised ~5% of the UKB population (>4,000 individuals), which may limit generalizability. This subgroup may also include individuals with atypical sleep or work schedules, introducing potential selection bias despite sufficient sample size for analysis. Third, there still may be residual and unmeasured confounding, such as meal timing. Finally, the generalizability of findings from UKB data are limited; however, corroborative results in the nationally representative NHANES data enhance the broader applicability of our conclusions.

In conclusion, when keeping total MVPA volume constant, clustering MVPA in the

afternoon-evening was associated with the strongest reduction in incident T2D risk, fewer prevalent diabetes, and more favorable glycemic measures.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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