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Timing of Moderate to Vigorous Physical Activity, Mortality, Cardiovascular Disease, and Microvascular Disease in Adults With Obesity

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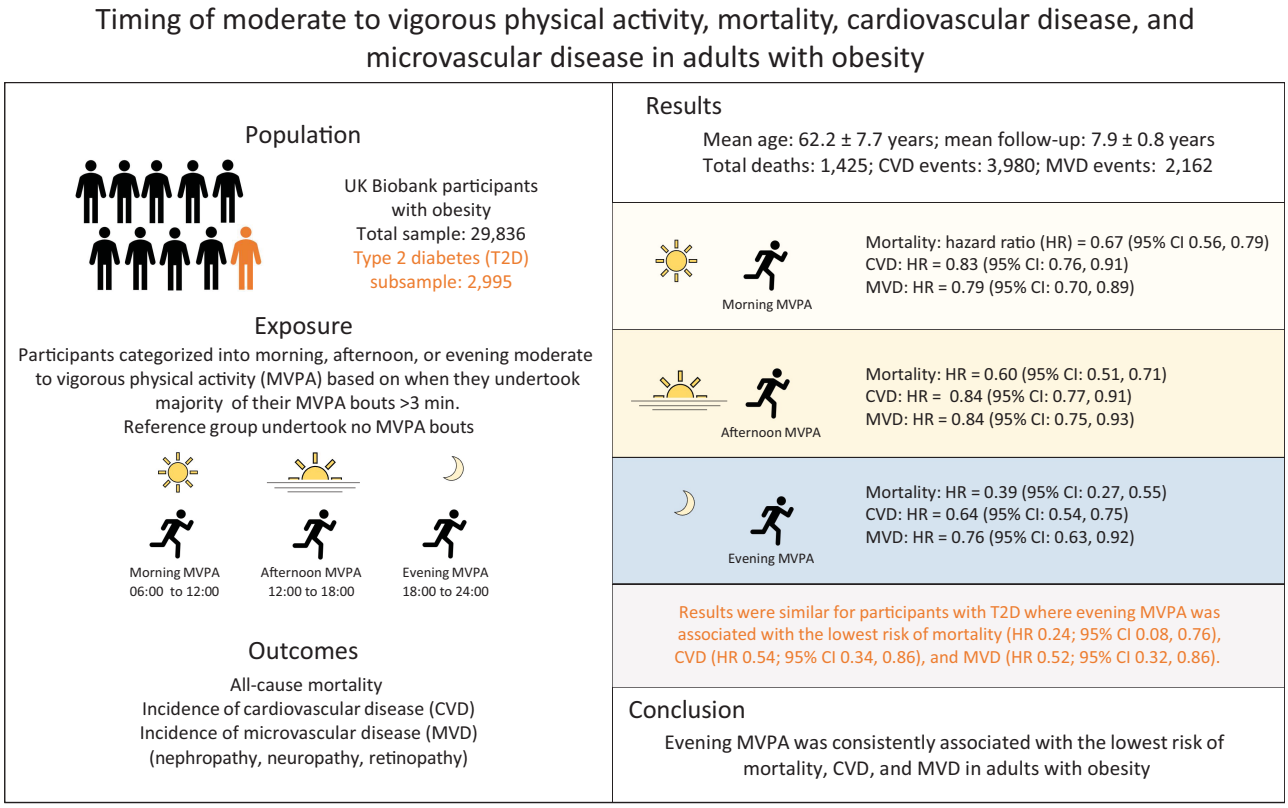

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Recent findings show that undertaking physical activity within specific time windows (e.g., morning, afternoon, or evening) may lead to greater improvements in cardiometabolic outcomes among individuals with or at risk of type 2 diabetes (T2D).
- **What is the specific question(s) we wanted to answer?**
  We sought to determine whether undertaking the majority of daily physical activity in the morning, afternoon, or evening was associated with mortality or cardiovascular morbidity.
- **What did we find?**
  The results showed that undertaking physical activity in the evening was associated with the lowest incidence of mortality and cardiovascular morbidity.
- **What are the implications of our findings?**
  The timing of physical activity may be an important consideration in the future of obesity and T2D management.

Timing of Moderate to Vigorous Physical Activity, Mortality, Cardiovascular Disease, and Microvascular Disease in Adults With Obesity

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ORIGINAL ARTICLE

OBJECTIVE

To assess the association between timing of aerobic moderate to vigorous physical activity (MVPA) and risk of cardiovascular disease (CVD), microvascular disease (MVD), and all-cause mortality in adults with obesity and a subset with obesity and type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

Participants included adults with obesity (BMI ≥30 kg/m^2) and a subset of those with T2D from the UK Biobank accelerometry substudy. Aerobic MVPA was defined as bouts of MVPA lasting ≧3 continuous minutes. Participants were categorized into morning, afternoon, or evening MVPA based on when they undertook the majority of their aerobic MVPA. The reference group included participants with an average of less than one aerobic MVPA bout per day. Analyses were adjusted for established and potential confounders.

RESULTS

The core sample included 29,836 adults with obesity, with a mean age of 62.2 (SD 7.7) years. Over a mean follow-up period of 7.9 (SD 0.8) years, 1,425 deaths, 3,980 CVD events, and 2,162 MVD events occurred. Compared with activity in the reference group, evening MVPA was associated with the lowest risk of mortality (hazard ratio [HR] 0.39; 95% CI 0.27, 0.55), whereas afternoon (HR 0.60; 95% CI 0.51, 0.71) and morning MVPA (HR 0.67; 95% CI 0.56, 0.79) demonstrated significant but weaker associations. Similar patterns were observed for CVD and MVD incidence, with evening MVPA associated with the lowest risk of CVD (HR 0.64; 95% CI 0.54, 0.75) and MVD (HR 0.76; 95% CI 0.63, 0.92). Findings were similar in the T2D subset (*n* = 2,995).

CONCLUSIONS

Aerobic MVPA bouts undertaken in the evening were associated with the lowest risk of mortality, CVD, and MVD. Timing of physical activity may play a role in the future of obesity and T2D management.

Obesity is a significant and independent risk factor for the development of type 2 diabetes (T2D) (1), cardiovascular disease (CVD), microvascular disease (MVD) (2), and premature mortality (3). These associations are fueled, in part, by obesity-related

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imbalances in adipokines, chronic inflammation, insulin resistance, and ensuing impaired glucose tolerance (4,5).

Engaging in moderate to vigorous physical activity (MVPA), particularly aerobic activity (6), is widely acknowledged as a therapeutic strategy for improving cardiometabolic risk factors (7). Although historically all MVPA, regardless of bout length, has been considered reflective of aerobic activity, very short MVPA bouts may not truly engage the aerobic energy system. Skeletal muscle predominantly relies on anaerobic energy pathways to meet sudden energy demand up to the first 3 min of MVPA, beyond which aerobic metabolism dominates (8). Recent evidence suggests that accumulating aerobic MVPA bouts is associated with a lower cardiovascular morbidity and mortality risk compared with accumulating shorter nonaerobic bouts (9).

Because obesity and T2D are associated with circadian misalignment and impaired metabolic processes (10), particularly during the evening (11), modulating the timing of MVPA may offset diurnal variations in glucose tolerance and insulin sensitivity (12), potentially leading to durable improvements in cardiovascular morbidity. Recent randomized trials have indicated that undertaking late-afternoon or evening aerobic exercise yields superior improvements in glucose control than that generated by morning aerobic exercise (13–15). However, it is unclear whether aerobic MVPA timing is associated with longer-term outcomes, such as morbidity and mortality, among individuals with exacerbated diurnal variations in glucose intolerance. Therefore, this study aimed to determine the association between the timing of MVPA, mortality, and incidence of CVD and MVD among adults with obesity and a subset also diagnosed with T2D.

RESEARCH DESIGN AND METHODS

Study Participants

This study included participants from the UK Biobank study, all of whom were enrolled between 2006 and 2010 and provided written informed consent. Ethical approval was obtained from the National Research Ethics Service of the U.K. National Health Service (NHS; ref. no. 11/NW/0382; London, U.K.). Participants underwent physical examinations conducted by trained staff and completed touchscreen questionnaires. The inclusion criteria were as follows: individuals with prevalent obesity (BMI $\geq$30 kg/m^2; ascertained through health linkage of general practitioner records), including those with T2D (ascertained through health linkage of medication prescription history, general practitioner records, and UK Biobank physical examination) (Supplementary Table 1). Exclusion criteria were as follows: individuals with missing covariate data or those experiencing an event within the initial 24 months of follow-up (9,16,17). In analyses considering CVD and MVD as outcomes, participants with prevalent CVD (ascertained through self-report and hospital admission records) or MVD (ascertained through hospital admission records) were excluded where appropriate (Supplementary Fig. 1).

Physical Activity Assessment

Between 2013 and 2015, a total of 103,684 participants wore an Axivity AX3 accelerometer (Axivity, Ltd, Newcastle Upon Tyne, U.K.) on their dominant wrist continuously for 24 h per day over a period of 7 days. Standard procedures were used for device calibration, and nonwear periods were detected using established methods (18). Participants with a minimum of 3 valid wear days, defined as wearing the accelerometer for at least 16 h per day, were included in the analysis. Physical activity intensity was determined in 10-s intervals using a validated machine-learning accelerometer-based two-level random forest classifier. Physical activity was first classified into one of four activity classes: sedentary, standing utilitarian movements (e.g., ironing a shirt, washing dishes), walking (e.g., active commuting, mopping floors), or running/high-energy activities (active play with children). These activity classes were then assigned to one of four activity intensities: sedentary, light, moderate, or vigorous (16,17,19). Walking activities were classified as light (an acceleration value of $<$100 mg), moderate ($\geq$100 mg), or vigorous ($\geq$400 mg) intensity. As described previously (9), this two-level physical activity classification scheme minimized the possibility of false-positive MVPA from stationary activities with high wrist movement, such as ironing or cleaning dishes, because an activity had to be classified first by level 1 as an ambulatory activity and then by level 2 as moderate or vigorous. Similar to in a previous study (20), to assess physical activity timing, participants were categorized into morning (6 A.M. to $<$12 P.M.), afternoon (12 P.M. to $<$6 P.M.), and evening MVPA (6 P.M. to $<$12 A.M.) groups based on when the majority of their MVPA occurred in bouts lasting $\geq$3 min (e.g., participants undertaking 40%, 30%, and 30% of their total MVPA bouts in the morning, afternoon, and evening, respectively, would be assigned to morning MVPA). Although a previous study categorized morning MVPA as 5 A.M. to 11 A.M., midday-afternoon MVPA as 11 A.M. to 5 P.M., and evening MVPA as 5 P.M. to 12 A.M. (21), we elected to categorize participants into one of three 6-h time windows, as per a previous study (20), to allow for three even 6-h timing windows. The choice of the $\geq$3-min bout length aimed to better capture aerobic-based MVPA, known for its established benefits in improving cardiometabolic health in adults with obesity (22), as well as its association with reduced cardiovascular risk (9). Participants who did not accumulate at least one MVPA bout lasting $\geq$3 min in the morning, afternoon, or evening were categorized as having no aerobic physical activity bouts, irrespective of the total minutes of physical activity accumulated. Additionally, we calculated the total time spent undertaking MVPA (regardless of bout length) and MVPA accrued from bouts lasting $<$3 min.

Mortality, CVD, and MVD Ascertainment

Participants were observed through to 30 November 2022, with deaths obtained through linkage with NHS Digital of England and Wales or the NHS Central Register and National Records of Scotland. Inpatient hospitalization data were sourced from the Hospital Episode Statistics for England, the Patient Episode Database for Wales, or the Scottish Morbidity Record for Scotland. Detailed methods for CVD and MVD assessment are outlined in Supplementary Table 2. In short, CVD was defined as a disease of the circulatory system, excluding hypertension and diseases of the arteries or lymph nodes (23). MVD was defined as neuropathy, nephropathy, or retinopathy (24). Follow-up time was calculated as the time in years from accelerometer wear to the first occurrence of event or censoring.

Covariates

Covariates considered in the analysis included age, sex, smoking status, alcohol intake, fruit and vegetable consumption, sedentary time, total MVPA, sleep duration, education, medication use (cholesterol, antihypertensive, and/or diabetes medication), waist circumference, and prevalent CVD (all-cause mortality analysis only). Complete definitions for all covariates are provided in Supplementary Table 3.

Analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% CIs for all-cause mortality. For CVD and MVD analyses, participants with prevalent CVD (ascertained through self-report and hospital admission records) or MVD (ascertained through hospital admission records) were excluded where appropriate. Additionally, the Fine-Gray subdistribution method was used, treating deaths resulting from non-CVD or non-MVD causes as competing risks when appropriate. Cox proportionality assumptions were assessed using Schoenfeld residuals, with no observed violations. The association between physical activity timing and risk of all-cause mortality, CVD, and MVD was examined, using the "no aerobic bouts" group as the referent. The analysis also included an examination of adjusted 5-year absolute risk and age- and sex-adjusted incidence rate ratios. A dose-response analysis of activity bout frequency and total duration per day was conducted using restricted cubic splines with knots at the 10th, 50th, and 90th percentiles, with the reference group set to zero bouts and minutes per day. Additionally, the association of physical activity timing with each outcome was explored among participants with T2D, with the no aerobic bouts group as the referent.

Sensitivity Analyses

To assess residual confounding, a negative control outcome of death or hospitalization resulting from an accident (excluding cycling, self-harm, and falls) was used as this outcome does not have an explicit mechanistic link to physical activity (25). If the negative control had an association pattern similar to that of the primary outcomes, it would be more plausible that the associations were due to bias and confounding than to causality. A sensitivity analysis for total mortality was conducted, excluding participants with prevalent CVD and cancer, recognizing that adjustment for prevalent disease may not fully capture confounding. Additional analyses were performed, categorizing the no aerobic bouts group based on meeting or not meeting physical activity guidelines (150 min of MVPA/week). Additional analyses included assessments for total MVPA and MVPA accrued from bouts lasting $<$3 min. To assess the influence of more even temporal distributions of aerobic MVPA, sensitivity analyses were conducted for mortality, CVD, and MVD incidence in which participants were only assigned to morning, afternoon, or evening MVPA if $>$50% of their total daily aerobic MVPA occurred during the same time window; otherwise, they were classified as having mixed MVPA, similar to in previous studies (21,26). Additional analyses were conducted, adjusting for LDL and HDL, blood pressure, ethnicity, Townsend deprivation index, season of accelerometer wear time, ethnicity, and employment status. To assess the influence of diet quality on the primary results, a sensitivity analysis was conducted using the dietary quality index (23). Finally, sensitivity analyses were also conducted to determine the association of the exposure with all outcomes among nonshift workers. All analyses were conducted using R statistical software, and reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guideline.

Data and Resource Availability

The UK Biobank data that support the findings of this study can be accessed by bona fide researchers when applying to access the UK Biobank research resource to conduct health-related research.

RESULTS

Our sample for all-cause mortality included 29,836 participants, with a mean age of 62.2 years (SD ±7.7) at baseline; 53.2% were female, and 46.8% were either current or previous smokers. A total of 2,995 participants had a prevalent T2D diagnosis at baseline. During an average follow-up time of 7.9 years (SD ±0.8), corresponding to 236,387 person-years, 1,425 deaths occurred. The sample for CVD analyses included 24,660 participants with 3,980 events, and the MVD analysis sample included 28,455 participants with 2,162 events (Supplementary Fig. 1). Throughout the week, participants in the reference group averaged fewer than one MVPA bout per day, whereas the morning MVPA group averaged 4.8 bouts per day in the morning, the afternoon MVPA group averaged 5.0 bouts per day in the afternoon, and the evening MVPA group averaged 3.4 bouts per day in the evening. Participant characteristics by physical activity timing group are listed in Table 1.

Adjusted 5-year absolute risk and incidence rate ratio are presented in Supplementary Table 4. The 5-year all-cause mortality risk was 25–32% lower for participants in the evening MVPA group (1.79%; 95% CI 2.31%, 1.27%) than for those in the morning (2.64%; 95% CI 3.08%, 2.21%) or afternoon MVPA (2.43%; 95% CI 2.81%, 2.05%) group. Participants in the reference group had a 5-year mortality risk of 4.02% (95% CI 4.48%, 3.57%). This pattern was consistent for the 5-year risk of CVD incidence. For MVD incidence, the 5-year risk was similar between morning, afternoon, and evening MVPA groups and 20–24% lower than that of the reference group (e.g., 5-year risk 5.86%; 95% CI 6.59%, 5.13% vs. 7.78%; 95% CI 8.44%, 7.12% for morning MVPA group vs. reference group). Supplementary Figs. 2 and 3 show the dose-response association for aerobic MVPA ($\geq$3 min) bout duration and frequency. Overall, the magnitude of association was stronger for activity bout frequency (e.g., nadir of the curve HR 0.39 for all-cause mortality) than for activity bout duration (nadir of the curve HR 0.59 for all-cause mortality).

All-Cause Mortality

Compared with the reference group, evening MVPA was associated with the lowest mortality risk (HR 0.39; 95% CI 0.27, 0.55) (Fig. 1). Mortality risk was similar for participants in the afternoon (HR 0.60; 95% CI 0.51, 0.71) and morning MVPA (HR 0.67; 95% CI 0.56, 0.79) groups. Among participants diagnosed with obesity and T2D, evening MVPA was again associated with the lowest mortality risk (HR 0.24; 95% CI 0.08, 0.76), followed by afternoon MVPA (HR 0.44; 95% CI 0.28, 0.72) (Supplementary Fig. 4). Notably, there was no observed association for participants in the morning MVPA (HR 0.86; 95% CI 0.57, 1.29) when compared with those in the reference group.

Table 1—Participant characteristics by physical activity timing group

	No aerobic bouts	Morning	Afternoon	Evening	Overall
Total *n*	15,530	5,452	6,949	1,905	29,836
Follow-up, years	7.9 (0.8)	7.9 (0.8)	7.8 (0.7)	7.9 (0.7)	7.9 (0.8)
Age, years	62.1 (7.7)	62.2 (7.8)	62.4 (7.7)	62.4 (7.7)	62.2 (7.7)
Male sex, *n* (%)	7,334 (47.2)	2,589 (47.5)	3,175 (45.7)	876 (46.0)	13,974 (46.8)
Aerobic MVPA bouts per day					
Morning	—	4.8 (5.4)	1.3 (2.6)	0.5 (1.2)	1.5 (3.4)
Afternoon	—	1.3 (2.5)	5.0 (5.6)	0.6 (1.4)	1.8 (3.7)
Evening	—	0.3 (1.2)	0.5 (1.3)	3.4 (3.5)	0.6 (1.8)
Aerobic MVPA bout length, min/bout		3.8 (3.2, 4.8)	3.7 (3.2, 4.6)	3.5 (3.0, 4.8)	3.5 (3.2, 4.8)
MVPA min/day	27.8 (15.8, 45.9)	27.6 (15.3, 46.4)	27.5 (15.5, 45.0)	29.1 (16.1, 45.8)	27.8 (15.6, 45.8)
Light intensity, min/day	99.9 (68.3, 152.5)	99.9 (67.7, 153.7)	100.1 (67.0,152.2)	98.9 (67.4, 155.1)	99.9 (67.9, 152.9)
Sedentary time, h/day	12.3 (11.2, 13.4)	12.3 (11.2, 13.4)	12.3 (11.2, 13.4)	12.4 (11.3, 13.3)	12.3 (11.2, 13.4)
Sleep duration, h/day	7.4 (6.5, 8.1)	7.4 (6.5, 8.2)	7.4 (6.5, 8.1)	7.4 (6.5, 8.1)	7.4 (6.5, 8.1)
Waist circumference, cm	96.6 (14.0)	96.7 (14.2)	96.5 (14.0)	96.3 (14.0)	96.6 (14.1)
Female	96.4 (14.0)	96.6 (14.2)	96.5 (14.2)	95.9 (13.9)	96.4 (14.1)
Male	96.9 (14.1)	96.8 (14.2)	96.4 (13.9)	96.7 (14.0)	96.7 (14.1)
Townsend deprivation index	−1.5 (2.9)	−1.5 (2.9)	−1.5 (2.9)	−1.6 (2.9)	−1.5 (2.9)
Alcohol consumption, *n* (%)					
Previous	503 (3.2)	192 (3.5)	209 (3.0)	67 (3.5)	971 (3.3)
Never	542 (3.5)	186 (3.4)	211 (3.0)	66 (3.5)	1,005 (3.4)
Within guidelines	8,749 (56.3)	3,058 (56.1)	3,985 (57.3)	1,090 (57.2)	16,882 (56.6)
Above guidelines	3,418 (22.0)	1,150 (21.1)	1,465 (21.1)	384 (20.2)	6,417 (21.5)
Doubly above guidelines	2,318 (14.9)	866 (15.9)	1,079 (15.5)	298 (15.6)	4,561 (15.3)
Smoking history, *n* (%)					
Never	8,340 (53.7)	2,886 (52.9)	3,654 (52.6)	994 (52.2)	15,874 (53.2)
Previous	6,049 (39.0)	2,192 (40.2)	2,783 (40.0)	769 (40.4)	11,793 (39.5)
Current	1,141 (7.3)	374 (6.9)	512 (7.4)	142 (7.5)	2,169 (7.3)
Fruit and vegetable servings per day	7.9 (4.6)	7.9 (4.6)	7.8 (4.6)	7.9 (4.5)	7.9 (4.6)
Prevalent CVD, *n* (%)	1,886 (12.1)	672 (12.3)	899 (12.9)	259 (13.6)	3,716 (12.5)
Prevalent cancer, *n* (%)	972 (6.3)	359 (6.6)	450 (6.5)	141 (7.4)	1,922 (6.4)
Medication use, *n* (%)					
Antihypertensive	4,031 (26.0)	1,424 (26.1)	1,818 (26.2)	498 (26.1)	7,771 (26.0)
Cholesterol	3,439 (22.1)	1,288 (23.6)	1,554 (22.4)	448 (23.5)	6,729 (22.6)
Insulin	1,227 (7.9)	353 (6.5)	431 (6.2)	127 (6.7)	2,138 (7.2)

Data are reported as mean (SD) or median (interquartile range) unless otherwise specified.

CVD Incidence

The findings for CVD incidence among participants with diagnosed obesity mirrored the pattern observed for all-cause mortality (Fig. 2). Evening MVPA was associated with the lowest CVD incidence risk (HR 0.64; 95% CI 0.54, 0.75). Morning MVPA was associated with a CVD incidence risk of 0.83 (95% CI 0.76, 0.91), and afternoon MVPA was associated with an incidence risk of 0.84 (95% CI 0.77, 0.91). Among participants with obesity and T2D, evening MVPA was associated with a CVD incidence risk of 0.54 (95% CI 0.34, 0.86), whereas morning and afternoon MVPA showed smaller or null associations, with HRs of 0.73 (95% CI 0.56, 0.94) and 0.85 (95% CI 0.69, 1.06), respectively (Supplementary Fig. 5).

MVD Incidence

Regarding the incidence of nephropathy, neuropathy, and retinopathy, we observed a similar magnitude of association across each of the three physical activity timing groups. Participants in the morning, afternoon, and evening MVPA groups had respective HRs of 0.79 (95% CI 0.70, 0.89), 0.84 (95% CI 0.75, 0.93), and 0.76 (95% CI 0.63, 0.92) (Fig. 3). Among participants with diagnosed T2D, the strength of association was greatest among those in the evening MVPA group (HR 0.52; 95% CI 0.32, 0.86), with null or smaller associations observed in the morning (HR 0.89; 95% CI 0.69, 1.14) and afternoon MVPA groups (HR 0.75; 95% CI 0.59, 0.95) (Supplementary Fig. 6).

Additional and Sensitivity Analyses

The analyses for negative control outcomes suggested that residual and unmeasured confounding likely had a minimal impact on the findings. Specifically, with the negative control outcome, the HR point estimate pattern was inconsistent relative to the main analyses, with no significant associations for any of the physical activity

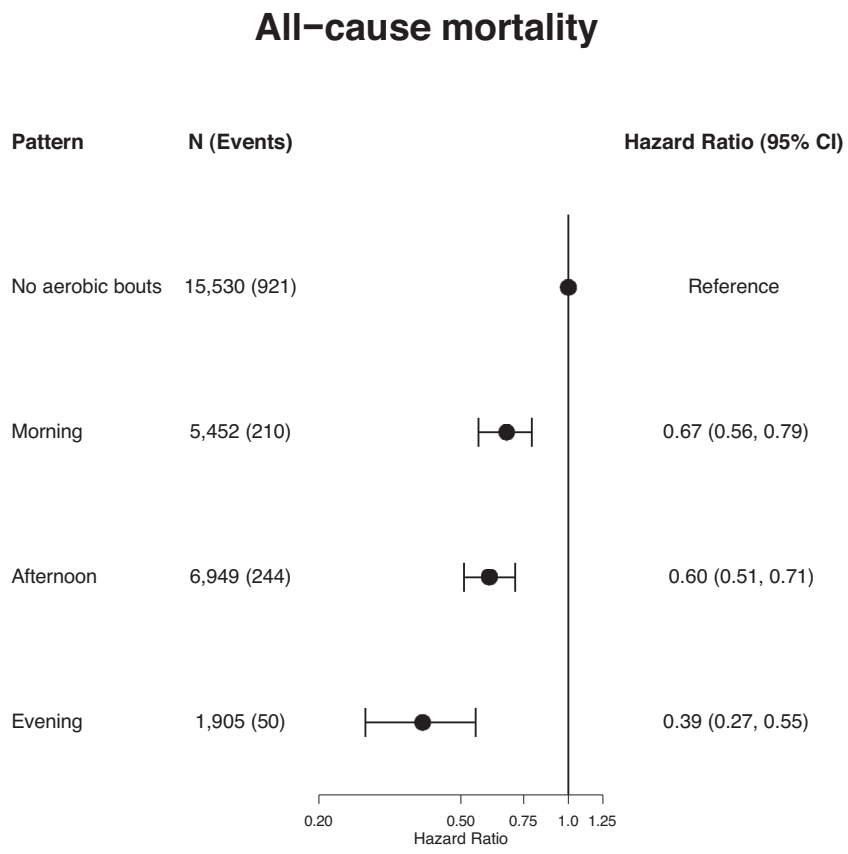

Figure 1—Association of aerobic MVPA bout (≥3 min) timing with all-cause mortality in adults with obesity. No aerobic bouts group represents participants who did not accumulate an average of one or more aerobic MVPA bout (≥3 min) per day over the week.

timing groups (Supplementary Fig. 7). Additional analyses controlling for LDL and HDL, blood pressure, ethnicity, Townsend deprivation index, season of accelerometer wear time, ethnicity, employment status, and diet quality index were consistent with our main analyses (Supplementary Tables 5 and 6). Consistent results for all-cause mortality were observed after excluding participants with prevalent CVD and cancer (n = 5,258) (Supplementary Fig. 8). The mortality risk ranged from 0.48 (95% CI 0.36, 0.65) for evening MVPA to 0.66 (95% CI 0.56, 0.78) for morning MVPA. Furthermore, separating the no aerobic bouts reference group into those meeting and not meeting physical activity guidelines (i.e., <150 min of MVPA/week) showed that meeting physical activity guidelines did not lower the risk of mortality or CVD or MVD incidence, if no aerobic bouts were undertaken (Supplementary Figs. 9, 10, and 11). Physical activity timing from bouts lasting <3 min was not associated with a lower risk of mortality or CVD or MVD incidence (Supplementary Figs. 12, 13, and 14). The sensitivity analyses in nonshift workers yielded consistent results (Supplementary Table 7). When undertaking sensitivity analyses to control for more even temporal distributions of aerobic MVPA (i.e., participants not undertaking >50% of total aerobic MVPA in one of the three time windows), the results showed that evening MVPA was associated with the lowest incidence rates in all outcomes relative to afternoon and morning MVPA, although similar to the primary analyses, there was little difference between timing groups for MVD. When compared with activity in the mixed MVPA group, evening MVPA was associated with the lowest risk of mortality, and with a similar incidence of CVD. Mixed MVPA was associated with the lowest incidence of MVD (Supplementary Figs. 15, 16, and 17). Finally, there was an inverse dose-response association between total MVPA, including both aerobic and nonaerobic bouts (any bout length), and all-cause mortality and CVD and MVD incidence (Supplementary Fig. 18).

CONCLUSIONS

Increasing MVPA is a proven strategy for effectively managing cardiometabolic risk in adults with obesity and related disorders. This study, to our knowledge, is the first to determine the associations between objectively measured aerobic MVPA timing, all-cause mortality, and incidence of CVD and MVD in adults with obesity. These findings demonstrate a compelling connection between MVPA timing and a lower risk of morbidity and mortality in adults with obesity, including those with T2D. Building upon previous clinical studies (14,15), our analyses underscore the consistent association of evening MVPA with the lowest risk in mortality, as well as strong associations with the incidence of CVD and MVD, when compared with not undertaking aerobic MVPA bouts. These findings are robust and extend to the subset of participants with T2D, in whom evening MVPA exhibited even more pronounced associations with mortality and cardiovascular morbidity. Sensitivity analyses demonstrated that when controlling for more even temporal distributions of aerobic MVPA, evening MVPA was associated with the greatest reduction in mortality, whereas more evenly spread MVPA was associated with the greatest reduction in MVD incidence. Finally, the frequency of aerobic bouts seems to be a more important factor in their association with mortality and CVD and MVD incidence than the duration of aerobic MVPA. Although additional well-designed clinical studies are required to confirm these findings, these observational data suggest that MVPA timing may play a significant role in optimizing MVPA-related interventions among adults contending with obesity and T2D.

Insulin resistance, a common feature in both obesity and T2D, denotes impairments in insulin-mediated processes such as glucose uptake, metabolism, and storage across diverse cell types, including adipocytes, hepatocytes, and skeletal muscle (27). Recognized as a key driver of obesity-related disease and aging (27,28), insulin resistance maintains an inverse association with mortality, independent of body weight (29). Although MVPA per se exhibits an inverse relationship with insulin resistance (30) and is linked to a lower mortality risk among individuals with or susceptible to T2D (31,32), the potential impact of undertaking MVPA during specific

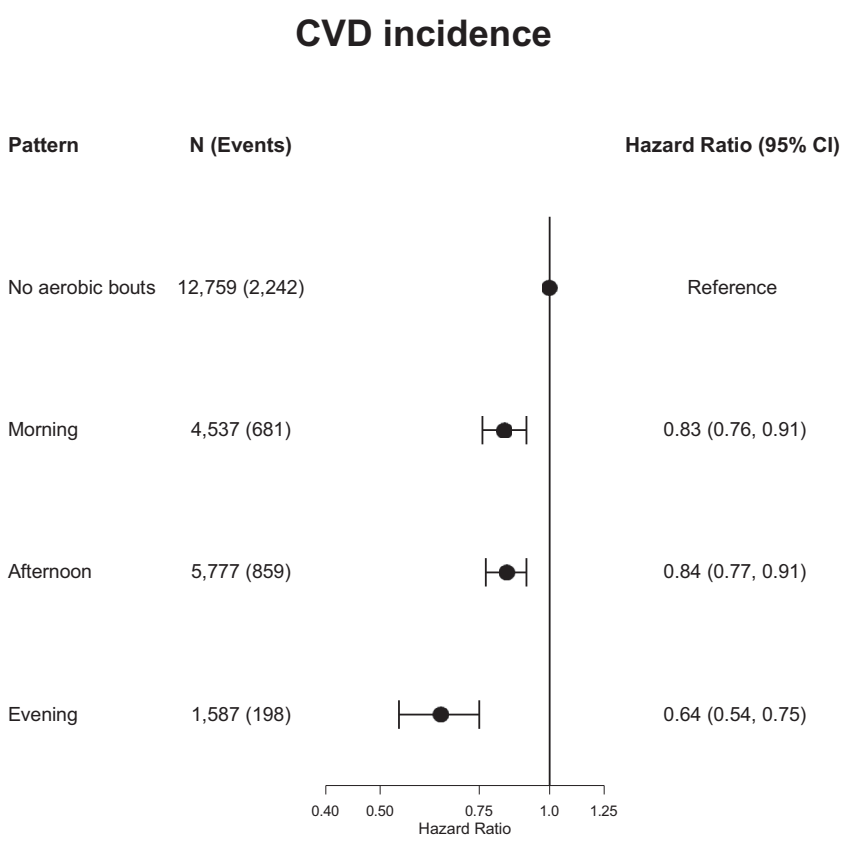

Figure 2—Association of aerobic MVPA bout (≥3 min) timing with the incidence of CVD in adults with obesity. No aerobic bouts group represents participants who did not accumulate an average of one or more aerobic MVPA bouts (≥3 min) per day over the week.

time windows on morbidity and mortality remains unclear. Previous findings have shown that MVPA performed in the evening is associated with the greatest improvement in insulin sensitivity (+25%) among adults with or without T2D (20). Our findings add to previous reports by showing that when controlling for total MVPA volume, the timing of MVPA, particularly in the evening, is linked with the lowest risk in all-cause mortality. Additionally, the frequency of aerobic MVPA bouts demonstrated a greater inverse association with mortality risk than the total volume of MVPA, highlighting that accumulating bouts of MVPA within specific timing windows or throughout the day may lead to improved health outcomes.

The robust findings of this study are in line with previously published cohort (20) and clinical studies (14,15). However, it is important to note that these findings differ from those of other similar studies (21). For example, a recent study by Feng et al. (21) showed that afternoon or mixed MVPA but not evening MVPA was associated with a lower mortality risk and CVD incidence than morning MVPA. These seemingly disparate findings may be explained by methodological differences. Firstly, Feng et al. selected morning MVPA as the reference group, whereas in our study, the reference group reflected individuals who did not undertake any aerobic MVPA. Furthermore, where our study focused on individuals with obesity, Feng et al. included individuals from the general population with and without obesity, which likely affected the results, given the association between obesity, circadian misalignment, and metabolic dysfunction (10,11). This may explain why, even when undertaking a sensitivity analysis to account for more even temporal distributions of MVPA, evening MVPA was still associated with a greater reduction in mortality and equal reduction in CVD incidence compared with activity in the mixed group.

Among adults with T2D, more than half of all deaths are related to CVD-related events, including myocardial infarction and ischemic stroke (33). The results of this study showed that when compared with other MVPA timing windows, evening MVPA was associated with the lowest incidence of CVD among adults with obesity, including those with T2D. Although further research is needed to uncover the precise mechanism behind this association, our findings align with previous studies indicating that moderate- or vigorous-intensity exercise performed in the evening may be linked to lower mean arterial blood pressure, whereas among morning exercisers, it was increased (34). Similarly, research suggests that evening, but not morning, aerobic exercise can lead to significant reductions in clinic and ambulatory blood pressure, through improvements in systemic vascular resistance and vasomotor sympathetic modulation, as demonstrated in a 10-week randomized trial involving 50 men with hypertension (35).

An important finding of this study was that aerobic MVPA, regardless of timing, was linked to a reduced risk of MVD. Although the sensitivity analyses revealed that mixed MVPA, followed by evening MVPA, was associated with the greatest reduction in MVD incidence, the differences between the timing windows (morning, afternoon, and evening) were minimal and nonsignificant. This finding highlights the role of MVPA in MVD prevention, and may be explained, in part, by the effects of MVPA on hyperglycemia and oxidative stress, which directly contribute to MVD development and progression (36). For example, findings from a previous clinical study demonstrated that moderate- to vigorous-intensity exercise directly improved microvascular function through improvements in redox balance via increased nitric oxide production (37). Furthermore, in addition to the well-established effects of chronic exercise on glycemia (38), it may be that more frequent episodes of contraction-stimulated glucose uptake into skeletal muscle may reduce hyperglycemic excursions throughout the day. This hypothesis is further supported by the significant association between frequency of MVPA and MVD demonstrated in our results. Thus, it seems plausible that these separate mechanistic pathways may have an additive interaction, thereby reducing the risk of MVD; however, additional studies are required to confirm this hypothesis.

For adults with obesity and T2D, where blood glucose regulation is an ongoing challenge, the results of this study highlight that

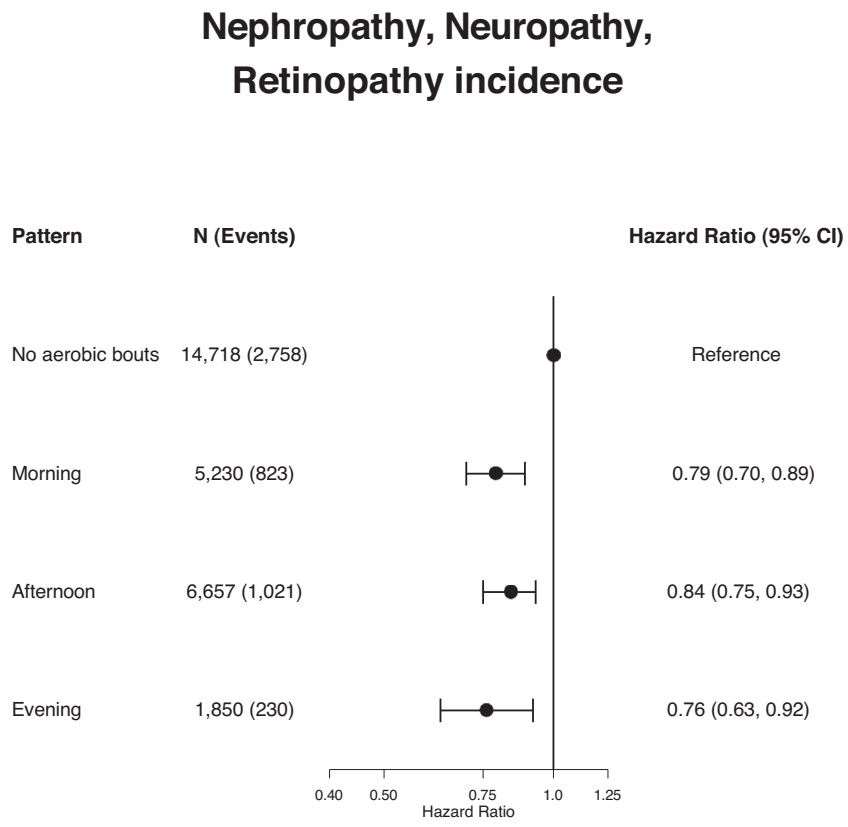

Figure 3—Association of aerobic MVPA bout (≥3 min) timing with the incidence of MVD in adults with obesity. No aerobic bouts group represents participants who did not accumulate an average of one or more aerobic MVPA bouts (≥3 min) per day over the week.

evening MVPA may yield the greatest benefits in terms of cardiovascular morbidity and mortality. Although the precise mechanisms driving this observation remain unclear, the concept of the dawn phenomenon, suggesting that T2D impairs the circadian rhythm, may offer insights. Individuals with T2D, partly due to desynchronized rhythms, often experience relatively better insulin sensitivity and glycemia in the evening, which progressively worsens overnight to the early morning (12,39). Therefore, engaging in MVPA later in the afternoon or evening, when postprandial glycemia is highest and hepatic insulin sensitivity begins to decline, may elicit the greatest metabolic benefits by directly influencing these pathways and leading to lower morning fasting glucose levels (12). Additionally, because β-cell function and glucose tolerance are reduced in the circadian evening (11), particularly in individuals with T2D, MVPA at this time may improve β-cell function when it is needed most. Additional well-designed clinical studies are required to delve deeper into these findings; however, this theory finds support, in part, in a recent prospective study and meta-analysis indicating that MVPA/exercise performed later in the day was associated with the greatest improvements in glucose control (13,40).

Strengths and Limitations

Strengths of our study include the large sample of participants with obesity and a subset concurrently diagnosed with T2D, which allowed for an in-depth exploration of associations with objectively measured physical activity timing using accelerometer-based wearable devices. The extended follow-up duration was instrumental in mitigating the risk of reverse causality by excluding participants with pre-existing CVD or MVD or events within the initial 2 years of follow-up. Despite these robust measures, the potential for reverse causation stemming from prodromal disease and unmeasured or residual confounding cannot be entirely ruled out because of the observational design of the study. However, our use of negative control outcomes suggests minimal impact on our observed associations. There was a median lag of 5.5 years between the UK Biobank baseline, when covariate measurements were taken, and the accelerometry study, although covariates remained generally stable over time, except for medication. The UK Biobank had a low response rate; however, previous work indicates that this factor of poor representativeness does not materially influence associations between physical activity and all-cause or CVD mortality (41).

Conclusion

In summary, our findings underscore the significant health benefits associated with evening MVPA among adults with or at risk of T2D. The results of this study emphasize that beyond the total volume of MVPA, its timing, particularly in the evening, was consistently associated with the lowest risk of mortality relative to other timing windows. Although future trials and device-based cohort studies are required to further explore MVPA timing as a potential factor in lifestyle interventions targeting cardiometabolic disease management, the available evidence suggests that evening MVPA may be a suitable therapeutic strategy.

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