It's about time: implications of chronoactivity on health and disease

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Part III

Chronoactivity and Mental Health

6

Association between device-based measured physical activity timing and depression risk: a prospective cohort study of UK Biobank participants.

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Abstract

Introduction

Physical activity (PA) decreases the risk of mental diseases. Although PA timing has been hypothesized to affect mental health outcomes, no largescale epidemiological cohort studies have been performed. We investigated the association between PA timing and incident depression in the general population.

Methods

A total of 89,934 European participants (62.4 ± 7.9 years, age range: 43-79 years, 44.8% men) without a history of depression were analysed. Hourly PA levels were derived from accelerometery data, and standardized for the total daily amount of PA. Participants were followed for a maximum of 8.5 years. Risk of incident depression dependent on individually standardized hourly PA level were assessed using Cox-proportional hazard models adjusted for potential confounders.

Results

During follow-up, 1,748 participants developed depression. Using the hourly standardized PA levels, we observed higher risk for incident depression with higher night-time PA (e.g., at 4:00 AM HR 1.35; 95%CI 1.28, 1.41), and lower depression risk with higher morning-time PA (e.g., at 9:00 AM HR 0.85; 0.81, 0.89). Also in the subgroup analysis, compared with participants who were most active during midday, participants with most PA in the early morning had a lower risk for incident depression (HR 0.80; 0.68, 0.95). No differences were observed when analyses were stratified for sex, chronotype, nor for the overall objective physical activity level.

Conclusions

Morning physical activity was associated with lower risk and night-time physical activity was associated with increased risk of depression. These findings may suggest future intervention studies should include timing as an additional dimension of physical activity as possible treatment and prevention strategy for depression.

Introduction

Depression is a major health threat amongst all age groups, with serious impact on the individual, society, and economy.(1) A growing body of evidence has shown that depression is an important risk factor for chronic (age-related) diseases such as dementia, Parkinson's disease, stroke, metabolic syndrome and coronary heart disease.(2, 3) Together with anxiety disorder, depression is the most common disabling mental disorder, and ranked 13th in a list of leading causes of burden worldwide.(4) Risk factors for depression include, among others, sleep-related and circadian disorders such as an advanced or delayed sleep phase, shift work, and a sedentary lifestyle.(5) Prevalence of these risk factors has increased markedly over the past decades due to our modern-day society that is fading the boundaries between day- and nighttime, creating an increased risk for depression and its implications on health.(6-8)

Physical activity and exercise are important non-pharmacological interventions for the prevention and treatment of depression.(9) Importantly, their (financial) burden is negligible and there is substantial scientific evidence that physical activity is effective for the prevention and treatment of depression among all age groups.(9, 10) One of the pathways explaining the positive effect of physical activity on depression can be found in the field of circadian medicine. Physical activity is an important yet relatively undervalued 'Zeitgeber'(11, 12): a cyclic environmental cue that can calibrate our internal clocks with each other and the environment. Changes in Zeitgeber behaviours (such as those that for example occur during shift work) can lead to circadian rhythm disruption which, in turn, has been associated with depression.(13, 14) Moreover, since circadian timing can be considered as the core function of the circadian clock system, timing of physical activity could possibly exert an additional advantageous effect. A growing research field has shown the additional effect of being physically active 'at the right time' for outcomes including cardiovascular disease, hypertension, metabolic health, and all-cause mortality.(15-23) In a recent systematic review, lower levels of physical activity early in the morning and higher levels of activity in the evening or night were found to be associated with higher occurrence of depression.(24) The authors emphasized the potential importance of the timing component of physical activity in the prevalence and incidence of depression/depressive symptoms. Yet they also concluded findings were mostly inconclusive and the sample sizes of most current studies were too small.

In this study, we aimed to contribute to current knowledge on the association between physical activity timing and depression incidence by performing a prospective observational study in a large population-based

cohort of middle aged and older adults. Based on the evidence of physical activity affecting both circadian function as well as depression risk, we hypothesized that timing of physical activity is an additional dimension associated with the risk of depression.

Methods

Study design and population

The data used for the current study was derived from UK Biobank, a large open-access population-based prospective cohort study including over 500,000 participants aged 40-69 years when recruited in 2006-2010.(25) Extensive phenotypic and genotypic details about its participants were and are still continuously collected across the entire United Kingdom with ongoing longitudinal follow-up for many health-related outcomes. De-identified data are made available for researchers that sign a material transfer agreement, undertaking to use data only for the purposes of the approved research and not to attempt to identify any participant in order to keep personal data secure. (25)

Between February 2013 and December 2015, a group of participants who had provided a valid email address were invited to wear an accelerometer for seven consecutive days. Participant email addresses were chosen randomly and participants were sent the accelerometer after accepting the invitation.(26) Accelerometery data was collected in a total of 103,684 participants. From this study sample, we excluded 3,223 (3.1%) participants because of data quality issues defined as: participants who either had less than three measurement days,(26, 27) had more than eight hourly acceleration values that equalled zero, or had unrealistically high acceleration values (daily mean acceleration adjusted for non-wear time bias equal to or more than 100 milligravity, mg). Additionally, we excluded 10,527 (10.2%) participants with a history of depression before data from the accelerometers was collected. Finally, 89,934 (86.7%) participants were included in the current analysis.

Assessment of physical activity

device-based measured data on physical activity was assessed using the Axivity AX3 wrist-worn triaxial accelerometer, a commercial version of the open source sensor Open Movement AX3 (https://github.com/digitalinteraction/openmovement) designed by Open Lab, Newcastle University.(26, 28) The device measured triaxial acceleration data over a 7 day period at 100

Hz with a dynamic range of ± 8 g. Calibration of the acceleration signals was performed as described before(28) to ensure similar output across devices.(26) Acceleration is presented in mg (1 mg=0.00981 m/s^2). Thresholds for activity intensities were: inactivity, < 30 mg; light, 30-99 mg; moderate, 100-399 mg; vigorous, ≥ 400 mg.(29) Participants were informed to wear the accelerometer continuously on their dominant wrist and to carry out their normal daily activities.

In this study, we used the 24-hour mean values from all measurement days. To classify participants into clusters based on the timing of their physical activity, we applied a data-driven K-means clustering approach. This is an unsupervised machine learning algorithm that partitions data into distinct clusters based on between-participant differences. It iteratively assigns data points to the nearest cluster centroid and updates centroids until convergence, minimizing within-cluster variance. (30) When we would have used the raw hourly mean acceleration as input, the clustering algorithm would primarily distinguish between individuals with generally high or low activity levels, rather than focusing on differences in activity timing. To ensure that our clusters reflected variations in activity timing rather than overall activity levels, we calculated relative acceleration. This was done by dividing each hourly mean acceleration by the individual's total daily mean acceleration, adjusting for potential bias due to non-wear time. This transformation allows for comparisons across individuals with different overall activity levels. A relative hourly acceleration value of 0.5 indicates that, during that hour, the participant was half as active as their daily average, while a value of 2.0 means they were twice as active compared to their overall daily mean. This approach ensures that the clustering captures variations in when participants were active, rather than how active they were in absolute terms.

Prior to the clustering analysis, a Within Sum of Squares (WSS) plot was made to determine the number of clusters with which the optimal intra- and inter-cluster variance was reached and thus should be taken into in the K-means analysis. After a visual inspection of the WSS, the K-means analysis was performed and the research group reached consensus about the interpretation of the derived clusters.(16)

Outcome variable

Information on depression was collected via multiple sources in the UK Biobank: self-report, data collected from the general practitioner, and linked Hospital Episode Statistics (HES) using ICD-10-CM code F32.(31) The follow-up period lasted from the accelerometer measurement period until November

2021 in which information depression incidence was collected. An incident diagnosis of depression was defined in the UK Biobank database as the date of the first occurrence of a reported depressive episode (data-field 130894) based on data derived from self-report, general practitioner, hospital admission and death registries, which ever came first.

Covariates

Body Mass Index (BMI)(32), chronotype(33, 34), number of taken treatments (medications), smoking status, alcohol intake, lifetime paternal and maternal depression history(35), season in which the accelerometer was worn, and socioeconomic status(36) (measured by the Townsend Deprivation Index, TDI) were considered to be possible confounding factors (model 2) next to age and sex (model 1). The age used in the current analyses was defined as baseline age and was calculated at the time participants wore the accelerometer. BMI was calculated at baseline using height and weight measurements. TDI is an index score defined at the moment of enrolment to the UK Biobank and is a composition of unemployment, non-ownership of a home, non-ownership of a car, and household overcrowding. TDI is not individual-specific but is linked to the participants postal code and is therefore a reflection of socioeconomic status (SES) of a neighbourhood. Positive values of the index will indicate areas with high material deprivation, whereas those with negative values will indicate relative affluence. A score of 0 represents an area with overall mean values.(37) Questionnaires were used to obtain data regarding number taken treatments, smoking status, alcohol intake, and maternal and paternal depression history. An online touchscreen at the study centre was used to collect self-reported data on sleep chronotype. Sleep chronotype was determined by asking: “do you consider yourself to be…” with the following answer options: 1) Definitely a morning person, 2) More a morning person than an evening person, 3) More an evening person than a morning person, 4) Definitely an evening person, 5) Do not know, 6) Prefer not to answer. All covariates except for season and age were collected at baseline of UK Biobank at one point between 2006 and 2010 which was three to nine years prior to the accelerometery data collection, depending on the participant. Season of accelerometer wear time was determined by the date of first wear, seasons were divided by the meteorological system.

Statistical analyses

Descriptive statistics were computed for the total population and for each chronoactivity cluster separately. Characteristics of the study population were

presented as mean (with standard deviation, SD) for continuous data or N (%) for categorical data.

As a first analysis we examined the associations between hourly mean relative physical activity (in SD units) and incident depression using Cox-proportional hazard analysis, adjusted for age and sex. Second, the clusters representing participants with different timing patterns determined from the K-means clustering were used as independent variables in the multivariable-adjusted Cox-proportional hazards regression models. The cluster representing an average relative acceleration pattern which best represented the average acceleration of the entire UK-Biobank accelerometery subgroup population and was the largest group, was used as reference. We used two models; model 1, in which we adjusted for age and sex, and model 2, in which we additionally adjusted for chronotype, BMI, number of taken treatments, TDI, smoking status, alcohol intake, depression mother, depression father, blood pressure medication, and lipid-lowering medication. Mortality and loss to follow-up data were available and used to censor individuals at their last recorded follow-up date to prevent bias in the estimation of disease-free survival.

In addition, we conducted stratified analysis by sex, mean daily physical activity level, by self-reported chronotype and socioeconomic status by TDI. Participants were divided into two similarly-sized PA groups based on the median value (notably 27.23 mg). For the analysis stratified by chronotype, we made two stratifications; one in which participants were divided into four groups according to the original questionnaire coding, and one in which participants were divided into two groups; morning chronotype (participants who characterized themselves as 'definitely a morning person' or 'more a morning person than an evening person'), and evening chronotype (participants who characterized themselves as 'definitely an evening person' or 'more an evening person than a morning person'). Participants who were classified as neither/unknown were excluded from these analyses. For the analyses stratified for SES we have also divided the population into two groups by a median split. This analysis was performed as a check for the degree of selection bias of the subgroup of the UK Biobank. It is known that the UK biobank population has a higher SES that the overall UK population.(38) Finally, we performed four sensitivity analyses in which we excluded the following participants; 1) with self-reported depression instead of an ICD-10 code, 2) who developed a depression within one year after their accelerometer measurement period to reduce the likelihood that activity pattern were influenced by undiagnosed depression or depressive symptoms as it is known that depression is a risk factor for increased sedentary behaviour , 3) with a history of an anxiety disorder (ICD-10-CM F40 and F41), and 4) who developed depression during

the COVID19 lockdown period (from 23 March 2020 in the UK) as it is plausible that this period simultaneously could have affected daily physical activity patterns and the risk of depression.(39) R v4.1.0 statistical software was used to perform all statistical analyses (R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org/).(40) Results are presented as the hazard ratio (HR) with accompanying 95% confidence interval (CI).

Results

Participant characteristics

Of the 89,934 participants without a history of depression included in this study (**Table 1**), the mean age was 62.4 (SD 7.9) years at the moment of the accelerometer data collection (age range: 43 to 79 years). The majority of the participants were women (55.2%). A total of 23,181 (25.8%) participants reported usual insomnia symptoms, and 8,082 (9%) reported maternal or paternal history of depression. Mean body weight of the study population was slightly overweight (mean BMI: 26.6, SD:4.4, kg/m^2), and 57.1% reported themselves as morning persons.

Table 1. Participant characteristics

	Total population
N	89,934
Age, mean (SD), years	62.4 (7.9)
Female sex, No. (%)	49,609 (55.2)
BMI, mean (SD), kg/m2	26.6 (4.4)
Average acceleration, mean (SD), mg	27.9 (8.6)
Season* (%)	
Winter	19,154 (21.3)
Spring	20,570 (22.9)
Summer	23,608 (26.3)
Autumn	26,602 (29.6)
Sleep chronotype, No. (%)	
Definitely morning persons	20,918 (23.3)
Intermediate morning persons	30,434 (33.9)
Intermediate evening persons	21,903 (24.4)
Definitely evening persons	7,155 (8)
Neither/unknown	9,524 (10.6)
Townsend Deprivation Index, mean (SD)	-1.76 (2.80)
Age completed education, mean (SD)	16.96 (2.71)

	Total population
Smoking status, No. (%)	
Never	51,658 (57.6)
Previous	32,097 (35.8)
Current	5,947 (6.6)
Alcohol intake frequency No. (%)	
Never	4,867 (8.4)
< 3x per week	32,292 (55.8)
≥ 3x per week	20,750 (35.8)
Depression father, No. (%)	2,894 (3.2)
Depression mother, No. (%)	5,188 (5.8)

BMI, body mass index; mg, milligravity;. Participant characteristics of the UK Biobank accelerometery subgroup.

* Season represents the season in which the accelerometer was worn.

Hourly relative physical activity in relation to depression incidence

During follow-up, 1,748 participants (1.9%) had an incident clinical diagnosis of depression. Depression risk patterns per hourly relative physical activity standardized mean are shown in **Figure 1A** (total accelerometery subgroup population), **1B** and **1C** (women, and men respectively). In the total population, high physical activity (relative to the total day mean) in the evening hours and at night (22:00-6:00) was associated with increased depression incidence (e.g., at 4:00 AM HR 1.35; 95%CI 1.28, 1.41). Contrarily, increased physical activity between 8:00-10:00 AM was associated with a lower incidence of depression (e.g., at 9:00 AM HR 0.85; 95%CI 0.81, 0.89). Stratified analyses for sex showed directionally similar results in men and women.

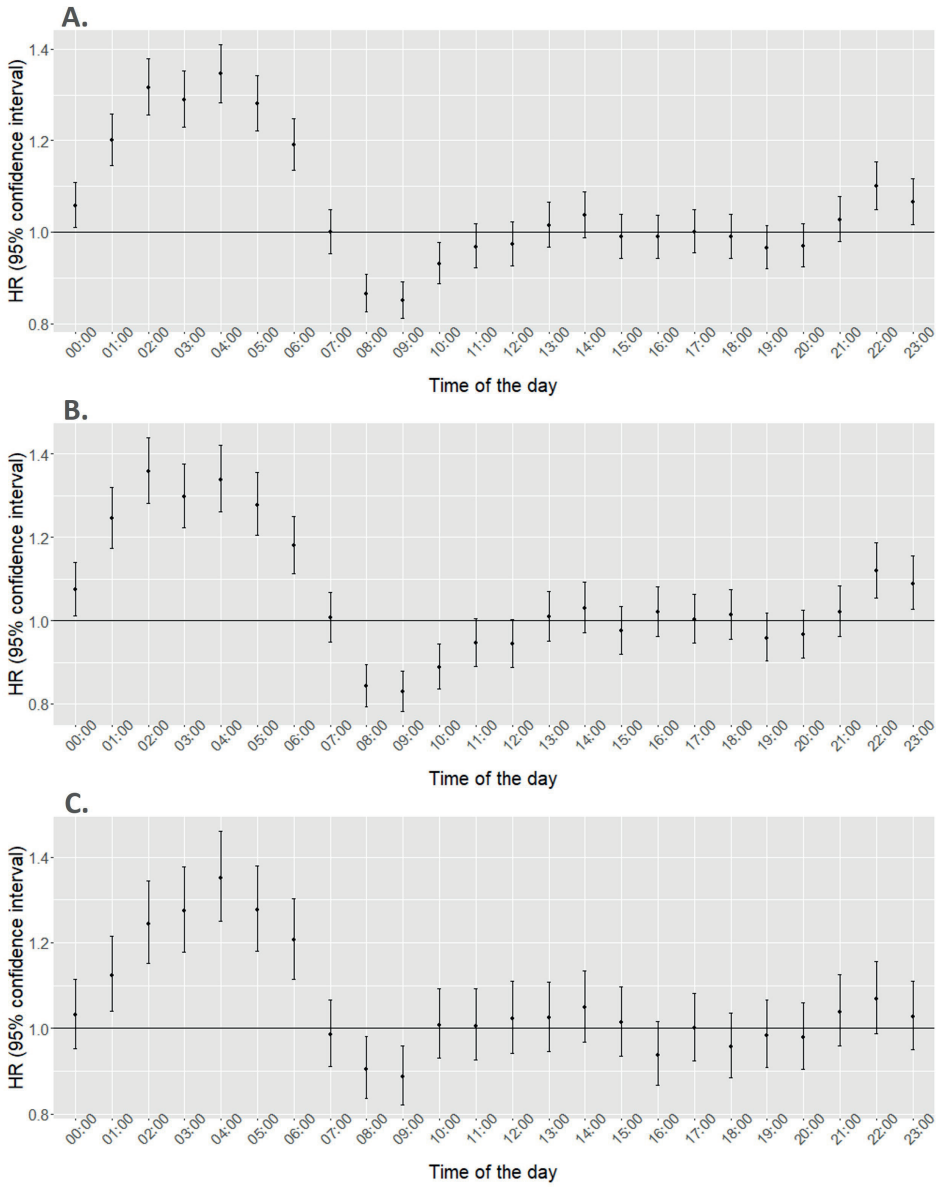

Figure 1. Hourly physical activity and depression risk pattern. Risk of depression per mean physical activity per hour. Cox-proportional hazard models were adjusted for age, sex, chronotype, body mass index (BMI), number of taken treatments, Townsend deprivation index (TDI), smoking status, alcohol intake frequency, paternal depression, and maternal depression (model 2). (A) shows the risk for the total accelerometery subgroup population, (B) shows the risk for women, and (C) shows the risk men.

Clusters of physical activity and their characteristics

The WSS plot is shown in **Supplementary figure 1**. **Figure 2** shows the chronoactivity for all four clusters. Cluster 1 was used as the reference in the regression analyses for reason that it had the largest sample size and it most closely reflects the average pattern of physical activity observed across the entire UK Biobank acceleration subgroup (**Supplementary figure 2**). Cluster 2 characterizes a subgroup of individuals exhibiting an early morning physical activity peak, while Cluster 3 captures a pattern of late morning physical activity peak. Cluster 4 represents a pattern of less activity during the day and an evening peak of physical activity. The baseline characteristics of the participants within each cluster are described in **Supplementary table 1**.

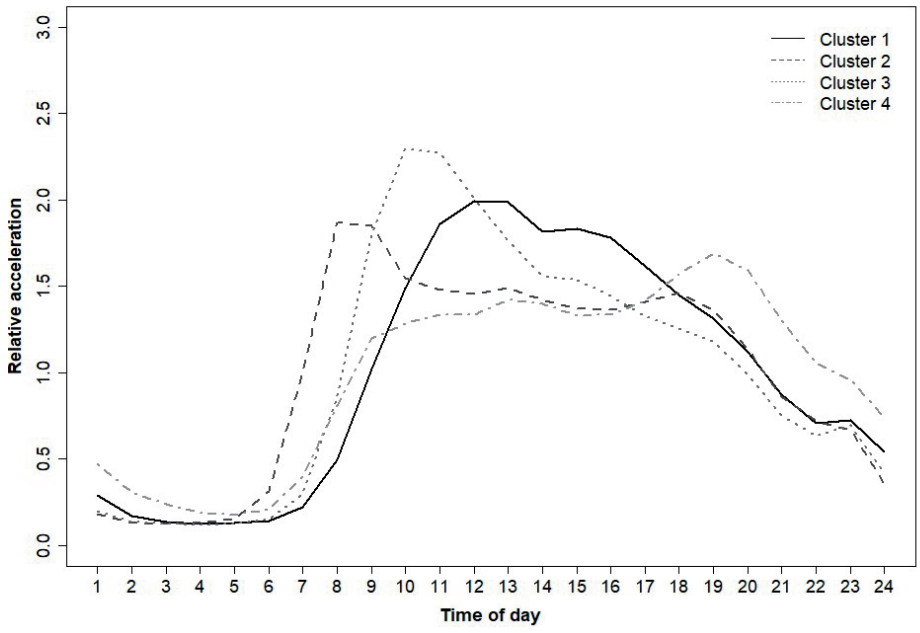

Figure 2. Pattern clusters of relative acceleration. Mean relative physical activity pattern per cluster. Relative acceleration shown in milligravity (mg). Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.

Figure 3 illustrates the associations between the clusters of physical activity timing and risk of incident depression. In the fully adjusted (model 2),

participants who were most active in the early morning (cluster 2) had a 20% lower risk of incident depression compared the participants who were most active during the midday (cluster 1) (HR 0.80; 95%CI 0.68, 0.95). Participants with a peak of physical activity in the late morning had an 21% lower risk of incident depression compared to the reference group (HR 0.79 95%CI 0.68, 0.93). We found no difference in risk for depression between the reference cluster and participants with a preference for their peak activity during early evening. Overall, the directions as well as the magnitude of the effect estimates remained similar for adjustment models 1 (**Supplementary table 2**) and 2. All associations remained similar when excluding self-reported depression cases, participants who developed a depression in the first year after accelerometery assessment, participants with a history of anxiety disorders, and participants who developed a depression during the COVID lockdown period (**Supplementary table 3**).

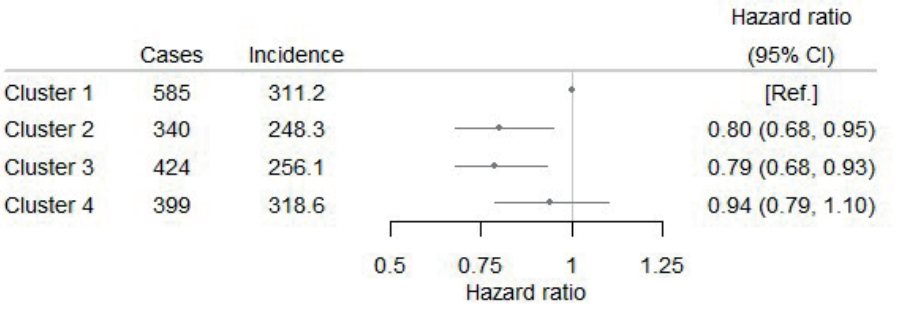

Figure 3. Associations between physical activity timing and incident depression. HR, Hazard Ratio; CI confidence interval. Hazard ratios depression incidence for every chrono-activity cluster in the total study population. Incidence was calculated per 100,000 person-years. Cox-proportional hazard models were adjusted for age, sex, chronotype, body mass index (BMI), number of taken treatments, Townsend deprivation index (TDI), smoking status, alcohol intake frequency, paternal depression, and maternal depression (model 2). Definitions clusters: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.

Stratified analyses

Supplementary table 4 shows associations for analyses stratified by sex, **Supplementary table 5** by total physical activity level, **Supplementary tables 6 and 7** by chronotype, and **Supplementary table 8** by SES. In total, 2.3% (1,118 cases) of all women included had incident depression during follow-

up versus 1.6% (630 cases) of all men. As expected(34, 41), we observed that incidence rates per 100,000 person-years were higher among less active people (compared to more active participants) as well as among evening chronotypes (compared to morning chronotypes) and participants with a lower SES. In general, all stratified analyses showed similar results as for the total population. Although some associations attenuated (e.g., in men and for more active participants), no evidence for interactions were found between groups in all stratification analyses (p-value for interaction >0.05).

Discussion

In this prospective cohort study, we observed distinct clusters of participants, each representing different patterns in the timing of their daily physical activity. Moreover, we observed that people whose physical activity peaked in the morning had a 21% lower risk for incident depression compared to people who were most active around midday. Physical activity is an essential non-pharmaceutical intervention for the prevention and treatment of depression disorders.(42) The present study adds to the previous evidence by demonstrating that timing of physical activity is independently associated with depression risk.

Multiple previous studies have investigated this association through cross-sectional and longitudinal observational study designs.(24, 43-45) For example, one study found less moderate to vigorous physical activity in the morning and less time in light physical activity throughout the day in people with prevalent depression than those without.(44) Another study found higher risk of incident depression in people with late timing of physical activity. (13) Additionally, studies found associations between high night-time physical activity as well as lower daily amplitude of activity rhythms and depressive symptoms.(13, 46) Yet, most of the current studies have small populations (up to 5,000 participants(44)) and low number of cases. Moreover, most studies within this field study how specific patterns of physical activity associate with depression cross-sectionally rather than to look at longitudinal associations. (45, 47) The present study, with a prospective study design and large number of included participants and number of cases therefore provides significant novel insights fuelling future studies.

Although there is a need for supporting evidence for the association between physical activity timing and depression incidence, several studies in mice and humans observed associations between physical activity timing and other health outcomes. For example, one study discovered that in mice

the timing of physical activity plays a crucial role in enhancing its beneficial effects on metabolic pathways in skeletal muscle and systemic energy homeostasis, which are linked to the incidence of cardiovascular disease (CVD).(20) Additionally, studies in humans found that midday moderate to vigorous physical activity (MVPA) was associated with a decreased all-cause mortality risk compared to morning MVPA.(23) Moreover, multiple studies showed that increased physical activity in the morning was associated with a lower risk of incident hypertension and poor (cardio) metabolic health.(15, 16, 21, 48) The growing interest in the impact of chronoactivity and the found associations with multiple health outcomes points to the potential importance of this dimension of physical activity.

Underlying mechanisms linking physical activity timing and a lower risk of depression are largely unknown. Recent literature does however show a clear association between physical activity timing and the circadian clock regulation and also between circadian clock regulation and mental health.(6, 12) In more detail, adults who perform more than one third of their total physical activity during the morning had a phase advance of approximately one hour of their sleep compared to those who do not.(11) Another study showed that adults with sleep disturbances have an increased risk for developing depression.(49) We hypothesize that the association that we observed between night-time activity and depression might be partially mediated through (lack of) sleep given the observations from previous studies on wakefulness after sleep onset and increased depressive symptoms.(50) Additionally, a systematic review concluded that there is sufficient evidence to support a role for physical activity as a 'Zeitgeber' for the human circadian system and, if timed appropriately, could be used to foster overall health.(12) Studies have shown that our skeletal muscles possess a strong, cell-autonomous circadian clock that could be enhanced or attenuated by timed behaviour.(51, 52) This peripheral clock plays an important role in the regulation of myokine secretion which in turn has been found to be associated with a depressed mood in middle-aged adults.(53) Future research should explore the causal pathways linking physical activity timing, circadian rhythm, sleep quality, and depression to better understand whether adjusting exercise timing could serve as a targeted intervention for preventing depression.

The relationship between depression and the circadian clock as well as the association between physical activity and depression is likely bidirectional.(6) Our data allowed for a longitudinal rather than a cross-sectional analysis. We also performed a sensitivity analysis for people who developed depression within one year after accelerometery data collection to reduce potential reverse

causation of yet present minor or subclinical depressive symptoms (that could influence 24-hour physical activity behaviour).

In this study, we also stratified our analysis by sleep chronotype. Previous research has established a strong association between evening chronotype and an increased risk of depression.(33, 34) One proposed explanation for this link involves genetic mutations in clock genes, which can lead to circadian disruption, altering the rhythmic activity of neurotransmitter systems involved in mood regulation and contributing to a preference for eveningness.(54) Additionally, sleep deprivation and circadian abnormalities—particularly delayed rhythms—are commonly observed in both evening chronotypes and individuals with depression.(54) Another contributing factor may be the societal bias toward morning-oriented schedules, which forces evening chronotypes to deviate from their intrinsic rhythms, potentially exacerbating their risk for mood disorders.(54) Notably, early-day light exposure is known to play a role in the prevention and treatment of depression, raising the question of whether evening chronotypes should align their behaviours with their natural rhythms or actively shift their schedules to increase morning light exposure. Our findings marginally support previous research suggesting that morning physical activity is associated with lower cardiovascular disease risk, irrespective of chronotype. Future studies should explore whether modifying the rest-activity patterns of evening chronotypes—such as encouraging earlier activity through behavioural interventions or melatonin supplementation—could serve as a viable intervention strategy.

The strengths of this study include its large sample size and cohort from UK Biobank. Also, physical activity was derived by accelerometers instead of subjective questionnaires collected in UK Biobank, and we used a data-driven clustering method to identify chronoactivity subgroups which is more likely to represent natural behavioural physical activity rhythms of the participants than predefined timing periods that have been used previously.(16) Finally, we were able to assess the relationship of physical activity timing in depression among sleep chronotype groups which is an important factor in depression risk.(34) The present study also has some limitations. First, a substantial proportion of invited participants did not respond to participate in the accelerometery subgroup study, which may introduce selection bias. As a result, the findings may not be generalizable to the broader population. However, our stratified analyses on SES did not differ from the total study population. These results suggest that although the UK Biobank consists of a selected population with a higher participation rate in people with a higher SES, the main study results are observed in both populations. The selected

population in UK Biobank therefore unlikely influenced the main results of the study. Second, data on chrononutrition (timing of food intake) and timing of light exposure—two other major Zeitgebers—was unavailable. These factors, along with physical activity, interact to influence circadian rhythms, sleep, and mental health.(12, 55) Additionally, the study sample was heterogeneous, including individuals with varying work schedules, parental responsibilities, and life circumstances, which likely influenced activity and sleep patterns. Without data on the timing and nature of physical activity or other behavioural patterns, it is difficult to determine the extent to which these additional Zeitgebers as well as other behaviours and environmental factors contributed to the observed associations. Given this complexity, future research should consider investigating more age-homogeneous groups to better understand sleep and activity timing patterns in specific life stages. Third, we did not have specific medication data and were unable to take for example antidepressants or benzodiazepine medications into account at the moment of data collection and start of the follow-up. We compensated for the absence of information by excluding individuals with history of depression as well as with a sensitivity analysis in which we excluded participants who developed a depression within one year and/or a history of anxiety. Fourth, participants characteristics and covariables were collected at baseline of the UK Biobank which was a few years before the accelerometery measurement period. This could possibly introduce some error and misclassification of the exposure at the moment of the accelerometers assessment. Finally, given the observational nature of this study, the possibility of residual confounding cannot be excluded, nor could the causal relationship underlying the association be thoroughly examined. These considerations should be carefully taken into account when interpreting the findings.

In conclusion, our study provides evidence that morning physical activity is associated with a lower risk of incident depression, independent of total physical activity. These findings may suggest future intervention studies should include timing as an additional dimension of physical activity as possible treatment and prevention strategy for depression.

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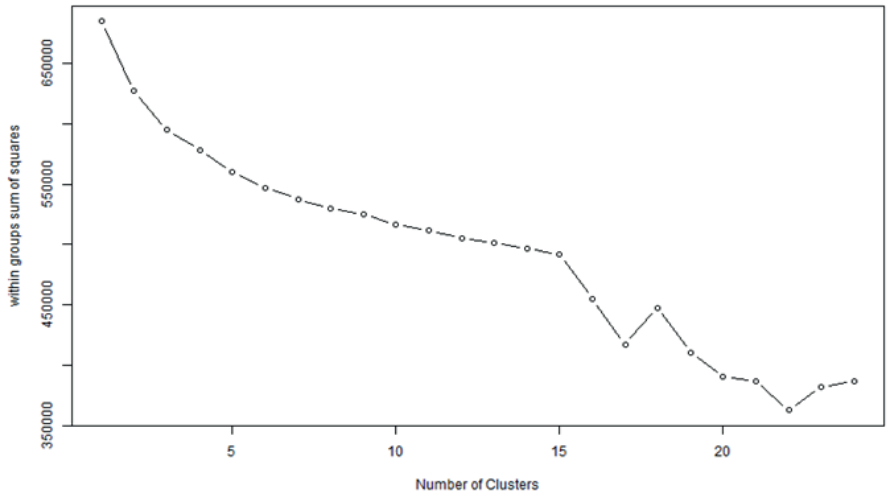
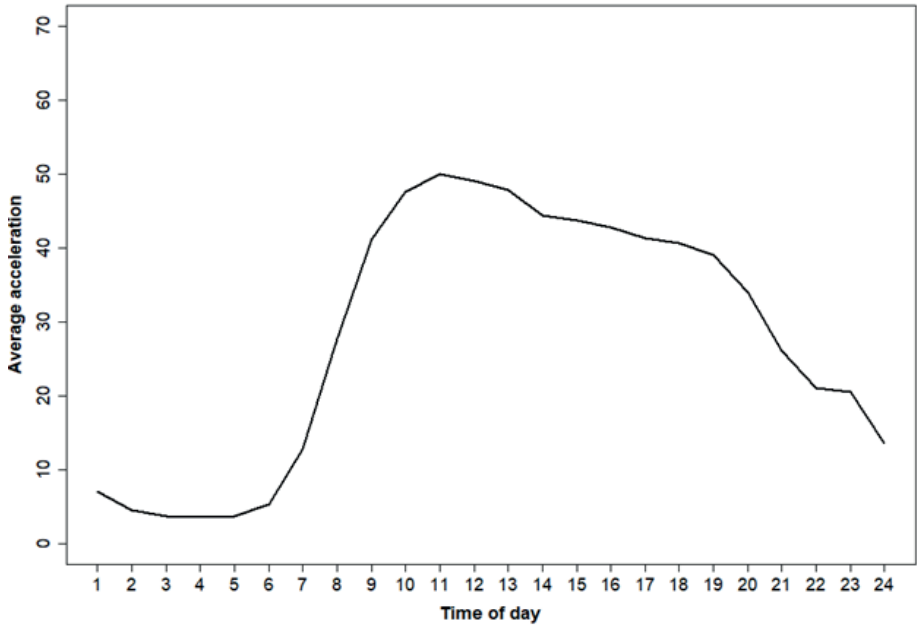
Appendix



Supplementary figure 1. Within Sum of Square plot. Within Sum of Squares plot to determine number of clusters for K-means clustering analysis. Finally, the number of clusters considered for clustering analysis was four.



Supplementary figure 2. Pattern of average acceleration. Pattern of mean daily acceleration of the total study group (N= 89,934) shown in milligravity (mg).

Supplementary table 1. Participant characteristics per cluster

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
N	27,591	19,843	24,262	18,238
Age, mean (SD), years	64.1 (7.1)	59.6 (7.9)	65.4 (6.9)	58.9 (7.8)
Female sex, No. (%)	15,093 (54.7)	10,801 (54.4)	13,867 (57.2)	9,848 (54)
BMI, mean (SD), kg/m2	26.8 (4.3)	26.6 (4.6)	26.5 (4.2)	26.6 (4.7)
Average acceleration, mean (SD), mg	27.3 (7.9)	29.3 (9.7)	27.6 (8.3)	27.8 (9.7)
Season* (%)				
Winter	6,036 (21.9)	3,960 (20.0)	5,655 (23.3)	3,503 (19.2)
Spring	6,218 (22.5)	4,924 (24.8)	5,238 (21.6)	4,190 (23.0)
Summer	7,049 (25.5)	5,086 (25.6)	5,985 (24.7)	5,488 (30.1)
Autumn	8,288 (30.0)	5,873 (29.6)	7,384 (30.4)	5,057 (27.7)
Sleep chronotype, No. (%)				
Definitely morning persons	4,610 (16.7)	6,781 (34.3)	6,862 (28.4)	2,665 (14.7)
Intermediate morning persons	8,773 (31.9)	7,274 (36.7)	9,279 (38.4)	5,108 (28.1)
Intermediate evening persons	8,243 (29.9)	3,284 (16.6)	4,609 (19.1)	5,767 (31.7)
Definitely evening persons	2,824 (10.3)	709 (3.6)	936 (3.9)	2,686 (14.8)
Neither/unknown	3,141 (11.4)	1,795 (9)	2,576 (10.6)	2,012 (11.1)
Townsend Deprivation Index, mean (SD)	-1.9 (2.7)	-1.55 (2.87)	-2.07 (2.62)	-1.36 (3)
Age completed education, mean (SD)	16.9 (2.7)	17 (2.8)	16.8 (2.6)	17.3 (2.9)
Smoking status, No. (%)				
Never	15,100 (54.9)	11,920 (60.2)	13,798 (57)	10,840 (59.6)
Previous	10,387 (37.7)	6,646 (33.6)	9,221 (38.1)	5,843 (32.1)
Current	2,036 (7.4)	1,230 (6.2)	1,170 (4.8)	1,511 (8.3)
Alcohol intake frequency No. (%)				
Never	1,267 (7.2)	1,221 (9.6)	1,293 (8.3)	1,086 (9.2)
< 3x per week	9,573 (54.1)	7,514 (58.9)	8,481 (54.4)	6,724 (56.8)
≥ 3x per week	6,856 (38.7)	4,033 (31.6)	5,826 (37.3)	4,035 (34.1)
Depression father, No. (%)	883 (3.2)	620 (3.1)	730 (3)	661 (3.6)
Depression mother, No. (%)	1,617 (5.9)	1,149 (5.8)	1,310 (5.4)	1,112 (6.1)

BMI, body mass index; mg, milligravity;. Participant characteristics of study population from the UK Biobank accelerometery subgroup per chronoactivity cluster. Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.

* Season represents the season in which the accelerometer was worn

Supplementary table 2. Hazard ratios for depression incidence by clusters model 1

	Cases	Incidence	Hazard Ratio (95% CI)
Cluster 1	585	311.2	[Ref.]
Cluster 2	340	248.3	0.79 (0.69, 0.91)
Cluster 3	424	256.1	0.82 (0.72, 0.93)
Cluster 4	399	318.6	1.02 (0.89, 1.16)

HR, Hazard Ratio; CI, confidence interval. Table shows outcomes from Cox-proportional hazard models adjusted for age and sex (model 1). Incidence was calculated per 100,000 person-years. Results represent the risk of depression compared to the reference group [Ref.] and are presented as hazard ratios with accompanying 95% confidence interval. Incidence was calculated per 100,000 person-years.

Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; 'early morning peak', cluster 3; 'late morning peak', cluster 4; 'evening peak'.

Supplementary table 3. Sensitivity analyses for depression risk by clusters

Activity level	Cases	Incidence	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)
Self-reported depression excluded				
Cluster 1	562	299	[Ref.]	[Ref.]
Cluster 2	304	222.1	0.75 (0.65, 0.87)	0.75 (0.63, 0.9)
Cluster 3	405	244.7	0.81 (0.71, 0.92)	0.77 (0.66, 0.91)
Cluster 4	370	295.6	1 (0.88, 1.15)	0.9 (0.76, 1.06)
Depression in years first excluded				
Cluster 1	505	268.7	[Ref.]	[Ref.]
Cluster 2	287	209.7	0.79 (0.68, 0.91)	0.77 (0.64, 0.93)
Cluster 3	372	224.7	0.83 (0.72, 0.95)	0.81 (0.69, 0.96)
Cluster 4	347	277.1	1.04 (0.91, 1.2)	0.94 (0.79, 1.12)
Individuals with history of anxiety excluded				
Cluster 1	511	281.1	[Ref.]	[Ref.]
Cluster 2	308	230.7	0.81 (0.7, 0.93)	0.81 (0.68, 0.97)
Cluster 3	373	232.1	0.82 (0.72, 0.94)	0.79 (0.67, 0.94)
Cluster 4	346	285.5	1 (0.87, 1.15)	0.94 (0.79, 1.12)
Follow-up until the first COVID-19 lockdown				
Cluster 1	467	325.3	[Ref.]	[Ref.]
Cluster 2	281	267.5	0.81 (0.69, 0.94)	0.81 (0.67, 0.98)
Cluster 3	330	261.1	0.8 (0.69, 0.92)	0.8 (0.67, 0.95)
Cluster 4	323	336.1	1.01 (0.88, 1.17)	0.95 (0.79, 1.14)

HR, Hazard Ratio; CI, confidence interval, Table shows outcomes from Cox-proportional hazard models adjusted for age and sex (model 1) and for chronotype, Body Mass Index (BMI), number of taken treatments (medications),Townsend Deprivation Index, smoking status, alcohol intake, season, maternal depression history and paternal depression history (model 2). Incidence was calculated per 100,000 person-years. Results represent the risk of depression compared to the reference group [Ref.] for four sensitivity analyses and are presented as hazard ratios with accompanying 95% confidence interval. 'Depression in first year' was defined as incident depression within 12 months after the accelerometer measurement week. Anxiety disorder was defined as ICD-10-CM F40 and F41. For the COVID-19 sensitivity analysis, follow-up was stopped on 23 March 2020. Incidence was calculated per 100,000 person-years.

Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; 'early morning peak', cluster 3; 'late morning peak', cluster 4; 'evening peak'.

Supplementary table 4. Depression risk by clusters stratified analysis by sex

	Sex	Cases	Incidence	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)	p-value for interaction
Cluster 1	Women	373	362.1	[Ref.]	[Ref.]	
	Men	212	249.5	[Ref.]	[Ref.]	
Cluster 2	Women	211	281.9	0.77 (0.65, 0.91)	0.78 (0.63, 0.97)	
	Men	129	207.8	0.83 (0.67, 1.04)	0.83 (0.63, 1.10)	0.69
Cluster 3	Women	264	277.9	0.77 (0.66, 0.90)	0.72 (0.59, 0.88)	
	Men	160	226.7	0.91 (0.74, 1.12)	0.93 (0.72, 1.20)	0.1
Cluster 4	Women	270	399.1	1.08 (0.92, 1.27)	0.94 (0.77, 1.15)	
	Men	129	224	0.89 (0.71, 1.12)	0.92 (0.70, 1.21)	0.98

HR, Hazard Ratio; CI, confidence interval. Table shows outcomes from Cox-proportional hazard models adjusted for age (model 1) and additionally adjusted for chronotype, Body Mass Index (BMI), number of taken treatments (medications),Townsend Deprivation Index, smoking status, alcohol intake, season, maternal depression history and paternal depression history (model 2) from stratified analyses for sex. Results represent the risk of depression compared to the reference group [Ref.] stratified by sex and are presented as hazard ratios with accompanying 95% confidence interval. P-values for interaction shown, $p<0.05$ indicates an effect interaction between groups. Incidence was calculated per 100,000 person-years. Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.

Supplementary table 5. Depression risk by clusters stratified analysis by activity level

	Activity level	Cases	Incidence	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)	p-value for interaction
Cluster 1	Less active	375	375.8	[Ref.]	[Ref.]	
	More active	210	238.1	[Ref.]	[Ref.]	
Cluster 2	Less active	159	272.4	0.71 (0.59, 0.86)	0.76 (0.61, 0.96)	
	More active	181	230.4	0.92 (0.76 ,1.13)	0.86 (0.67, 1.11)	0.33
Cluster 3	Less active	255	294.9	0.79 (0.68, 0.93)	0.79 (0.65, 0.96)	
	More active	169	213.7	0.89 (0.73, 1.09)	0.81 (0.62, 1.05)	0.86
Cluster 4	Less active	239	398.1	1.03 (0.87, 1.22)	0.97 (0.79, 1.20)	
	More active	160	245.4	0.98 (0.79, 1.21)	0.86 (0.66, 1.13)	0.54

HR, Hazard Ratio; CI, confidence interval. Table shows outcomes from Cox-proportional hazard models adjusted for age and sex (model 1) and additionally adjusted for chronotype, Body Mass Index (BMI), number of taken treatments (medications),Townsend Deprivation Index, smoking status, alcohol intake, season, maternal depression history and paternal depression history (model 2) from stratified analyses for total physical activity level. Results represent the risk of depression compared to the reference group [Ref.] stratified by activity level and are presented as hazard ratios with accompanying 95% confidence interval. Participants were divided into two groups representing lower and higher levels of total physical activity by a median spilt (median activity level was 27.2 milligravity). P-values for interaction shown, $p<0.05$ indicates an effect interaction between groups. Incidence was calculated per 100,000 person-years. Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.

Supplementary table 6. Depression risk by clusters stratified analysis by chronotype (four categories)

	Chronotype	Cases	Incidence	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)
Cluster 1	Definitely morning	107	341	[Ref.]	[Ref.]
	Intermediate morning	170	283.9	[Ref.]	[Ref.]
	Intermediate evening	177	315.2	[Ref.]	[Ref.]
	Definitely evening	78	405.3	[Ref.]	[Ref.]
Cluster 2	Definitely morning	121	259.3	0.75 (0.58, 0.98)	0.65 (0.47, 0.90)
	Intermediate morning	122	242.7	0.86 (0.68, 1.10)	0.84 (0.63, 1.12)
	Intermediate evening	60	264.6	0.83 (0.61, 1.12)	1.00 (0.70, 1.45)
	Definitely evening	12	243.3	0.58 (0.31, 1.08)	0.66 (0.32, 1.38)
Cluster 3	Definitely morning	121	258.2	0.75 (0.58, 0.97)	0.67 (0.48, 0.92)
	Intermediate morning	150	236.8	0.83 (0.66, 1.03)	0.67 (0.51, 0.89)
	Intermediate evening	92	293.2	0.93 (0.72, 1.20)	1.09 (0.79, 1.49)
	Definitely evening	17	266.2	0.66 (0.39, 1.11)	0.61 (0.30, 1.25)
Cluster 4	Definitely morning	58	317.3	0.92 (0.66, 1.27)	0.74 (0.49, 1.11)
	Intermediate morning	96	273	0.97 (0.75, 1.25)	0.90 (0.66, 1.23)
	Intermediate evening	135	341.1	1.06 (0.84, 1.35)	1.22 (0.92, 1.63)
	Definitely evening	66	358.1	0.85 (0.61, 1.20)	0.70 (0.45, 1.09)

HR, Hazard Ratio; CI, confidence interval. Table shows outcomes from Cox-proportional hazard models adjusted for age and sex (model 1) and additionally adjusted for Body Mass Index (BMI), number of taken treatments (medications),Townsend Deprivation Index, smoking status, alcohol intake, season, maternal depression history and paternal depression history (model 2) from stratified analyses for chronotype. Results represent the risk of depression compared to the reference group [Ref.] stratified by chronotype and are presented as hazard ratios with accompanying 95% confidence interval. P-values for interaction shown, $p<0.05$ indicates an effect interaction between groups. Incidence was calculated per 100,000 person-years. Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.

Supplementary table 7. Depression risk by clusters stratified analysis by chronotype (two categories)

	Chronotype	Cases	Incidence	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)	p-value for interaction
Cluster 1	Morning	277	303.5	[Ref.]	[Ref.]	
	Evening	255	338.2	[Ref.]	[Ref.]	
Cluster 2	Morning	243	250.7	0.82 (0.69, 0.98)	0.75 (0.60, 0.92)	
	Evening	72	260.8	0.76 (0.58, 0.99)	0.93 (0.67, 1.27)	0.69
Cluster 3	Morning	271	245.9	0.80 (0.68, 0.95)	0.68 (0.55, 0.84)	
	Evening	109	288.7	0.86 (0.68, 1.07)	0.98 (0.74, 1.30)	0.06
Cluster 4	Morning	154	288.1	0.95 (0.78, 1.16)	0.83 (0.65, 1.06)	
	Evening	201	346.5	1.00 (0.83, 1.21)	1.04 (0.82, 1.33)	0.14

HR, Hazard Ratio; CI, confidence interval. Table shows outcomes from Cox-proportional hazard models adjusted for age and sex (model 1) and additionally adjusted for Body Mass Index (BMI), number of taken treatments (medications),Townsend Deprivation Index, smoking status, alcohol intake, season, maternal depression history and paternal depression history (model 2) from stratified analyses for chronotype. Results represent the risk of depression compared to the reference group [Ref.] stratified by chronotype and are presented as hazard ratios with accompanying 95% confidence interval. Participants were divided into two groups representing chronotype. the group 'morning chronotype' contained participants who classified themselves as 'definitively morning person' or 'more a morning person than an evening person' and the 'evening chronotype' group contained participants who considered themselves to be 'definitely evening person' or 'more an evening person than a morning person'. P-values for interaction shown, $p<0.05$ indicates an effect interaction between groups. Incidence was calculated per 100,000 person-years. Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.

Supplementary table 8. Depression risk by clusters stratified analysis by socioeconomic status (Townsend Deprivation Index)

	SES	Cases	Incidence	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)	p-value for interaction
Cluster 1	Low SES	310	343.2	[Ref.]	[Ref.]	
	High SES	274	281.2	[Ref.]	[Ref.]	
Cluster 2	Low SES	210	288.8	0.80 (0.67, 0.96)	0.85 (0.68, 1.06)	
	High SES	130	203	0.77 (0.62, 0.95)	0.73 (0.56, 0.96)	0.12
Cluster 3	Low SES	228	303.4	0.89 (0.75, 1.06)	0.89 (0.72, 1.10)	
	High SES	196	217.2	0.75 (0.62, 0.90)	0.68 (0.54, 0.87)	0.16
Cluster 4	Low SES	244	351.9	0.98 (0.82, 1.16)	0.89 (0.72, 1.10)	
	High SES	155	278	1.06 (0.87, 1.30)	1.03 (0.80, 1.32)	0.85

HR, Hazard Ratio; CI, confidence interval. Table shows outcomes from Cox-proportional hazard models adjusted for age and sex (model 1) and additionally adjusted for chronotype, Body Mass Index (BMI), number of taken treatments (medications), smoking status, alcohol intake, season, maternal depression history and paternal depression history (model 2) from stratified analyses for total physical activity level. Results represent the risk of depression compared to the reference group [Ref.] stratified by socioeconomic status as measured by the Townsend Deprivation Index (TDI) and are presented as hazard ratios with accompanying 95% confidence interval. Groups were divided in two by a median spilt (median TDI was -2.4 points) P-values for interaction shown, $p<0.05$ indicates an effect interaction between groups. Incidence was calculated per 100,000 person-years. Definitions cluster: cluster 1; average pattern of acceleration close to the average pattern of absolute acceleration of the total UK Biobank accelerometery subgroup population, cluster 2; early morning peak, cluster 3; late morning peak, cluster 4; evening peak.