Article title: The association of the most active 30-minute continuous physical activity timing, midpoint of sleep timing and glycated haemoglobin levels (HbA1c)

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Abstract:

The growing cases of type 2 diabetes mellitus is a concerning growth worldwide. The study used, identified 675 usable participants from the CODEC study. The study analysed the association between midpoint of sleep, most active 30-minutes of continuous physical activity timing and glycated hemoglobin. The main tools used for data analysis was a GENEActiv accelerometer, and statistical analysis was conducted through SPSS (version 26). To analyse data, a participant needed at least 16-hours of clean data, over a 24-hour period. The results identified no significant difference between midpoint of sleep, physical activity timing and HbA1c. However, there was a significant difference in examining age and sleep ($p = .012$), alongside age and physical activity timing ($p = .010$). Furthermore, when splitting the age groups (overs 60s vs under 60s), it resulted in no significant. There is clear evidence that more research needs to be conducted.

Introduction:

The main role of insulin within the human body is to move glucose into the inside of the cells. When the affinity of insulin binding to cells is diminished, for example, the same amount of insulin is produced however, there is less effectiveness in binding to the cells, this causes there to be a surge of signaling which triggers GLUT4 translocation and glucose absorption out of the bloodstream. This results in more insulin needed to ensure the same level of glucose uptake – creating high blood sugar levels, this is further known as a disease called “Type 2 Diabetes Mellitus” (T2DM; Defronzo et al., 2015). Within the United Kingdom (UK), there is approximately 3.9 million people suffering from diabetes, with >1 million more undiagnosed (Diabetes UK, 2019). Furthermore, in the United States of America (USA), there is approximately 34 million people with diabetes (90-95% being type 2), (diabetes UK, 2019).

It was postulated by Connolly et al., (2000) that lower socioeconomic status (SES) played a primary role in the prevalence of diabetes within the UK, there was no evidence on the association between type 1 diabetes and socioeconomic status, but there was clear
evidence between type 2 diabetes and deprivation. Furthermore, it was also identified that within deprived areas, the approximate age for type 2 diabetes to occur is from the age of 40 years (Connolly et al., 2000). Many people in lower SES areas may be undiagnosed with the disease too, as within the deprived areas there is less chance of seeing primary care specialists. Furthermore, more people miss appointments in these areas, therefore less screening is conducted to detect dysglycaemia or elevated glycated haemoglobin levels (HbA1c).

HbA1c, where haemoglobin and sugars (specifically monosaccharides, like; glucose, galactose, and fructose) join. The normal range for HbA1c values is 4-5.6%, then for someone living with diabetes the range is 5.7-6.4% and finally, when a patient’s value is >6.4%, they have too much sugar in the bloodstream and will be diagnosed with diabetes (DeFronzo et al., 2015).

A strong way to control HbA1c levels in someone living with diabetes and someone who is not, is to monitor diet and eat more low glycaemic index foods, for instance, chickpeas, green vegetables, seafood, brown rice. This prevents the blood sugar levels rapidly increasing, because the foods allow carbohydrates to be broken down slowly, therefore, allowing more control over HbA1c and eventually tighter regulations of blood glucose, reducing hyperglycemic-related complications.

Midpoint of sleep can be defined as the clock time between the onset of sleep and final waking time (Randler et al., 2019). Obtaining a later midpoint of sleep (late chronotype) impacts a person’s lifestyle negatively in many ways. Firstly, a study designed by Facer-Childs et al., (2018) established that later chronotypes have poorer cognitive performance. Later midpoints of sleep means increased daytime sleepiness, this is linked to alertness and execution of general daily functions being worsened. Furthermore, it increases the chances of patient’s developing addictions to caffeine and potentially alcohol to try and improve their cognitive functions and energy levels (Stein and Friedmann, 2009). Moreover, the effects of being a late chronotype negatively impacts the circadian rhythm, this is in the suprachiasmatic nucleus (SCN) within the anterior hypothalamus in the brain – meaning organs need to work harder throughout the day and
night (Mazri, et al., 2020). This type of behavior is associated with detrimental health and psychological consequences/outcomes, such as, cardiovascular disease.

Chronotypes which have a later midpoint of sleep, are associated with elevated HbA1c levels (Anothaisintawee et al., 2017). A factor related to this increased value, is breakfast skipping. Breakfast skipping increases glycated haemoglobin, because when awaking, the body needs calories and nutrients to form energy (Mazri, et al., 2020. However, if the body does not receive these nutrients, then throughout the day the body will gradually need more calories. This will increase the chances of the patient overeating, (Reutrakal et al., 2014). With the potential increased in number of calories per day, this can lead to the chances of developing obesity, furthermore cardiovascular diseases (like diabetes). This will inevitably lead to poor control of Hba1c levels and promote worsened diabetes, (Reutrakal et al., 2014).

Furthermore, alongside physical problems caused from late midpoints of sleep, psychological issues such as depression, anxiety and insomnia may occur. These psychological problems impact eating habits, alcohol consumption and lack of physical activity. This is linked to worsening glycated haemoglobin control because it promotes patients eating more unhealthy foods, which inevitably increases the blood sugar levels and being physically inactive increases the insulin resistance, meaning the body has no control over the type 2 diabetes (Leontis and Hess-Fischl, 2021).

The World Health Organization (WHO) state that adults ages 18-64 need a minimum of 150 minutes of moderate physical activity or 75 minutes of vigorous physical, per week. Regular physical activity benefits the human body physiologically by, reducing triglycerides in the blood, reducing low-density lipoproteins (further increase high-density lipoproteins) and improving insulin resistance. Furthermore, physical activity helps people psychologically too, by reducing anxiety, stress, and depression symptoms.

Linking Hba1C values to regular physical activity showed positive outcomes across previous research. A study by Najafipour et al., (2017) established regular long-term physical activity improved glycaemic control, body composition and cardiovascular fitness among patients- further identifying that some type 2 diabetics have reversed their disease. Furthermore, Boniol et al., (2017) identified that increasing physical activity by
100 minutes, per week, created a reduction in HbA1c results by -0.14%, however these results did not stipulate whether this was maintained across all age groups, different genders and different ethnicities.

There is limited evidence on whether the specific timing of physical activity makes a bigger impact on HbA1c levels and more research needs to be designed to investigate. However, a study by Teo et al., (2019) stated that the timing of physical activity made no impact on the HbA1c, so long as the activity was performed consistently at that time.

The aim of the study was to examine association between the physical activity and midpoint of sleep timing, with glycated haemoglobin levels (HbA1c). It was predicted that later midpoints of sleep and later physical activity timings, with a positive association on the HbA1c level.

Methods:

Study Design

The study was a cross-sectional data analysis using the data from the CODEC study, which was designed to investigate chronotypes of patients with type 2 diabetes and the association with glycaemic control (Brady et al., 2019). Ethical approval was granted from the West Midlands- Black Country Research Ethics Committee (16/WM/0457). All participants completed a written informed consent.

Participants

Participants were recruited from both primary and secondary care settings from four sites across the Midlands area, UK (Leicester, Nottingham, Derby, Northampton). Participants who were interested returned a reply slip to the research team. Telephone screening to confirm the inclusion and exclusion criteria was then conducted. Inclusion criteria included:

- Established Type 2 Diabetes (>6 months since diagnosis)
- Participants to be aged 18-75
- Females and males
• No known sleeping disorders, except for Obstructive Sleep Apnea
• HbA1c to be 10% than or equal to 86mmol/mol
• BMI>45kg/m²

Participants who met the inclusion criteria were booked for the study consent and measurements visit.

Measures

Demographics and Anthropometrics

Demographic variables consisted of age, sex, employment, ethnicity, family history of diabetes or related diseases and any medication prescribed were collected through an interview administered questionnaire. Within the clinical session, height, weight, BMI, waist circumference and neck circumference were also measured. Height was measured by using the Leicester Height Measure, which is a free-standing, plastic stadiometer, the unit of the results was written to the nearest Centimeters. Alongside this a bioimpedance analysis, including weight variables and BMI, were conducted through a TANITA body composition monitor (SA165A-095OU-3, Sino-American Electronics, Co ltd, Taiwan), the unit of the results was in Kilograms.

Accelerometer-assessed Physical Activity

Participants were requested to wear the GENEActiv accelerometer (Activinsights Ltd, Kimbolton, UK) 24 hours for 8 days. The monitor was also initialized with a sampling frequency of 100Hz, set for midnight on the night of the clinic visit and finish 8 days later. Prior to analysis, the data was categorized to determine the subjects who did not wear the monitor. The accelerometer data were cleaned and processed through the R package in GGIR. This processed the multi-day raw data (expressed in m/s², also known as the gravitational acceleration), primarily used for physical activity and sleep research. The process included automatic calibration, it alerted the researcher of any abnormal high readings, detected a subject who did not wear the monitor and calculation of average magnitude of dynamic acceleration.
Generally, the monitor measured per day, per segment of the day and the estimated value of physical activity, inactivity and sleep (Hees, 2020). The variables of interest associated with the physical activity aspect, was the time of day that each participant produced their most active continuous 30 minutes physical activity across a 24-hour period. A valid day for the ability to analyze, was ensuring a subject had at least 16 hours of data per day.

**Midpoint of sleep**

Midpoint of sleep was calculated using data from the GENEActiv accelerometer. It was calculated as the midpoint of sleep, which was derived from the onset and duration of sleep to calculate the middle time (Randler et al., 2019).

**Glycaemic Control**

Participants were asked to fast for at least 4 hours, besides water, prior to the clinic visit. A blood sample was taken via venipuncture to measure glycated haemoglobin (HbA1c).

**Analysis**

Data analysis was conducted through a Statistical software called, SPSS (version 26). A linear regression test was used to examine the association between physical activity and midpoint of sleep with HbA1c. The model was adjusted for sex, ethnicity, BMI and age to ensure the results were independent of these factors (further analysis was conducted to notice any more in-depth association between over 60s and under 60s, and physical activity, midpoint of sleep and HbA1c). Two tests were then performed which were; physical activity time and Hba1c percentage and the midpoint of sleep time and HbA1c percentage.

**Results**

In total, 675 participants from the CODEC study provide valid measures for most continuous 30-minute physical activity timing, midpoint of sleep timing and glycated haemoglobin levels were included in the analysis. Participants were 65% males, 80% white European with a mean age of 63 ± 8.41 years. Table 1 presents the participant's characteristics. The physical activity variable measured was the 'most continuous 30 minutes of physical activity’, this was the time that an individual performed continuous
activity for 30 minutes, within a 24-hour day, ensuring the individual had at least 16 hours of valid data. Furthermore, the sleep variable measured was ‘midpoint of sleep’, this was the middle point of time between onset of sleep and actual wake time.

Table 1: Participant Characteristics (mean ± standard deviation)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=675</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>63 ± 8.41</td>
</tr>
<tr>
<td>Male (%)</td>
<td>65%</td>
</tr>
<tr>
<td>Female (%)</td>
<td>35%</td>
</tr>
<tr>
<td>White Ethnicity (%)</td>
<td>80%</td>
</tr>
<tr>
<td>Other Ethnicities (%)</td>
<td>20%</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2%</td>
</tr>
<tr>
<td>Height (m)</td>
<td>170.09 ± 9.98</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>90.20 ± 17.76</td>
</tr>
<tr>
<td>BMI (kg.m^2)</td>
<td>31.01 ± 5.12</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>108.1 ± 13.47</td>
</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>41.2 ± 4.3</td>
</tr>
<tr>
<td>Most continuous 30 minutes of physical activity</td>
<td>12:06 ± 2.10</td>
</tr>
<tr>
<td>Midpoint of sleep</td>
<td>03:23 ± 1.15</td>
</tr>
<tr>
<td>Sleep Duration (average)</td>
<td>6 hours 13 mins</td>
</tr>
<tr>
<td>Acceleration (average)</td>
<td>14:06±50.41</td>
</tr>
</tbody>
</table>

There were no significant associations between the timing of the most active continuous 30 minutes of physical activity, or the midpoint of sleep and HbA1c levels, see table 2. However, it was discovered there was a significant association between age and the midpoint of sleep ($p = .012$), alongside age and the time of physical activity ($p = .010$).
Table 2: Regression results for association between physical activity and HbA1c and midpoint of sleep and HbA1c.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>.003</td>
<td>.891</td>
</tr>
<tr>
<td>Midpoint of sleep</td>
<td>-.004</td>
<td>.921</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>.010</td>
<td>.187</td>
</tr>
<tr>
<td>Midpoint of sleep</td>
<td>-.001</td>
<td>.109</td>
</tr>
</tbody>
</table>

*Model 1 was adjusted for age, ethnicity, sex, and BMI.

Results from model 1 demonstrated the only group with a significant association to midpoint of sleep, physical activity and HbA1c was age. After further analysis into the sub-groups of age (over 60 and under 60), it resulted in there being no association between over 60’s, physical activity and HbA1c (p = .571) and under 60’s, physical activity and HbA1c (p = .475). Furthermore, there was no association between over 60’s, midpoint of sleep and HbA1c (p = .592) or under 60’s, midpoint of sleep and Hba1c (p = .525).

Discussion
The aim of the study was to examine the association between the timing of continuous 30 minutes physical activity and midpoint of sleep to glycated haemoglobin levels (HbA1c). If it was determined that physical activity and sleep timings made an impact on
healthier glycated haemoglobin levels, it would allow a more beneficial way to allow patients with type 1 and type 2 diabetes gain more control over their HbA1c levels, more specifically, allow type 2 diabetic patients to potentially recover from the disease.

Analysis of the results determined the main outcomes to be non-significant, further remaining non-significant after adjustments for measures of BMI, age, sex and ethnicity. Interestingly, age was shown to have a strong significant association with both physical activity and midpoint of sleep variables, however when further splitting age into sub-groups (over 60s vs under 60s) there was no association.

The average midpoint of sleep timing in this study was 03:23am, this corresponds with previous research by Brouwer et al., (2020), where the results produced an average time of 03:20am. Conversely, Brouwer et al., (2020) also identified that, midpoint of sleep established a higher HbA1c level in patients who perceived poor sleep efficiency. When establishing the significant association with midpoint of sleep, physical activity timing and HbA1c in the specific variable – age, it corresponded with Brouwer et al., (2020) who determined age to be the variable that most affected the glycated haemoglobin. Additionally, a study by Kelly et al., (2020) also established age to be a strong indication of higher glycated haemoglobin levels, specifically the younger generation obtaining a higher HbA1c result. Comparing against Kelly et al., (2020), their study identified a strong significant association between obtaining a later midpoint of sleep and increase in glycated haemoglobin level, however, this was determined in the specific patients who had a social jetlag of >90 minutes. There was no association in ≤90 minutes. This primarily resulted due to the poor level of the circadian rhythm, for instance; consistently experiencing later onset or sleep or later actual waking time, and not providing the body’s systems with a structured sleep pattern.

The concerns related to later chronotypes are that the circadian system is negatively impacted (a mismatch between the social rhythms and circadian clock), this is where the primary source of glucose metabolism occurs.
When evaluating the reasoning of the association between later chronotypes obtaining a higher HbA1c value, it was established from multiple studies that the main characteristic associated was social jetlag (Larcher et al., 2016). Unfortunately, there is no clear evidence on the specific factors of social jetlag that cause HbA1c to increase. However, a main outcome affected by being a late chronotype is a patient’s circadian rhythm. The circadian rhythm is the wake-sleep cycle over a 24-hour period, and it can influence sleep, body temperature, hormones, and appetite (Walker et al., 2020). Two of the main negative outcomes that effect the circadian cycle are, glucose tolerance and the decrease in insulin sensitivity (nhs.co.uk, 2021). When the body obtains low insulin sensitivity, it causes excess pressure onto the pancreas to increase the insulin production, resulting in blood sugar clearance to be quicker- consequently, this could result in hyperinsulinemia (nhs.co.uk, 2021). Hyperinsulinemia is linked to increasing the chances of, damaging blood vessels, heart failure, osteoporosis, and cancer (Ormazabal et al., 2018). Further effects from the circadian cycle include, increase postprandial glucose levels, this is primarily due to inadequate pancreatic β - cell function (Hellerstrom. 1984). The β – cell is in the islets of the pancreas, where their main role is to secrete and synthesize insulin and amylin. When the cells function and amount is impacted, it will lead to poor insulin secretion and eventually hyperglycaemia (Hellerstrom, 1984). A beneficial process to control insulin secretion, synthesis, and general glucose metabolism, is to consume more low glycaemic index foods. As previously discussed, this allows the body to slowly breakdown carbohydrates to ensure blood sugars levels due to rapidly rise.

Physical inactivity is responsible for 7% of deaths caused from diabetes, worldwide (Nakamura et al., 2017). The average time when patients participated in 30 minutes of physical activity for this study was 12:06pm, however as established, there was no significant association between physical activity timing and HbA1c – besides the variable, age. A study performed by McCarthy et al., (2017) contrasted with this study, where it was discovered that with a 30-minute increase of physical activity per day, was associated with a decrease of 0.11% (1.2mmol/mol) in HbA1c. In comparison, an increase in 6kg body weight, meant an increase of 0.8% (0.9mmol/mol) in HbA1c. Both results conclude
in a disagreement with this study, as McCarthy et al., (2017) determined a significant association between physical activity and glycated haemoglobin. Furthermore, in disagreement with the results of this study, Umpierre et al., (2011) identified that when type 2 diabetic patients increase their weekly physical activity time by more than 150 minutes (per week) it reduced their HbA1c level by approximately 0.89%. The study performed by Umpierre et al., (2011) also found there was a significant association between physical activity and HbA1c ($p < 0.001$).

During the analysis of whether physical activity and HbA1c have a significant association, it was examined the amount of exercise regularly engaged within, and it was established >150 minutes physical activity per week reduces HbA1c values by -0.36%, (Umpierre et al., 2011). Church et al., (2011) determined the most beneficial exercise to reduce HbA1c levels is, combining aerobic and resistance training. Moreover, Bweir et al, (2009) established the comparison between resistance and aerobic training showed, resistance training reduced HbA1c more than aerobic. Resistance training benefits diabetic patients and their HbA1c levels because the increased role of glucose within the muscles allows an increase in contractile-mediated insulin intake and has long term benefits. For example, increase fat free mass (Bweir et al., 2009).

There is currently limited evidence on whether participating in physical activity at later times throughout the day, increases HbA1c, when comparing to physical activity within the early hours of the day. However, this study discovered a non-significant association between physical activity timing and HbA1c. The only evidence through previous research is that, to align with your circadian rhythm, participating at the same time consistently each day will provide benefits to reducing HbA1c eventually.

The strengths from the cross-sectional analysis allowed the data to be specific patients who suffered from type 2 diabetes, whilst ensuring there is a range of ethnicities, sexes, and ages, to be representatives of the population. One of the main strengths was, the study gathered data from four areas of the UK. This meant the data was not specific to a particular area, therefore we could gather analysis of lifestyle behaviours from different
areas – furthermore, this made the results more generalizable to the wider population. Another strength from the study, was it allowed a range of ages (18–75). This ensured the data was varied in physical ability, for instance; more active vs non-active and health issues vs no health issues, allowing a more in-depth analysis into different lifestyles. Due to the wide age range and range of physical activity levels which strengthened the data, this links to the physical activity variable within the study as it influences whether exercise does impact HbA1c, how much exercise is good for reducing HbA1c and the mode of exercise too. The final strength of the study was all patients were type 2 diabetics. This allowed the data to follow the specificity point, where it’s easier to analyse data and it helps strengthen the evidence base used when developing type 2 diabetes mellitus prevention strategies.

The first limitation of this study was, it did not justify results for factors like sleep quality, sleep efficiency and any medical issues (for instance; sleep apnea). This provides a negative effect on the study as there could have been more analysis to see whether those who had higher sleep quality, produced a better association with HbA1c, and same for sleep efficiency. Furthermore, examining sleep duration with the association of HbA1c allows researchers to know the desired amount of sleep for each age group or specific person. The other limitation to the study was all the patients were type 2 diabetics. This provides a limitation as, if the study has been type 2 diabetics against non-diabetic patients, it would give a bigger analysis on whether physical activity and midpoint of sleep provide a specific effect on one group, then a different effect for the other group. It also provides evidence on whether physical activity and midpoint of sleep benefits non-diabetic patients too, whilst seeing whether is aids prevention of type 2 diabetes.

Future research needs to be conducted to see whether timing of physical activity aids the prevention of type 2 diabetes, more specifically, to see whether participating in physical activity earlier in the day is healthier than later in the day. In addition, there needs to be more research in comparing diabetic patients to non-diabetic patients’ midpoint of sleep and physical activity, and the association with HbA1c. This will enable a more precise analysis on what encourages HbA1c to lower, and how a patient can gain stronger control
over blood sugar levels. Finally, more analysis into how age effects HbA1c levels (in diabetic and non-diabetic patients), would allow a stronger idea on which age group is mainly affected by a rapid increase in blood sugar levels, and potentially find a cause for this. Furthermore, this research can be used to determine better physical activity regimens for older aged people, who are more sedentary.

**Conclusion**

The aim of this study was to examine association between the physical activity and midpoint of sleep timing, with glycaated haemoglobin levels (HbA1c). The purpose was to see whether participating in physical activity earlier in the day, and obtaining an earlier midpoint of sleep, reduced HbA1c levels. Midpoint of sleep and HbA1c provided no significant association and physical activity timing and HbA1c, also provided no significant association. However, when doing further analysis, it was noticed that age produced significant associations with HbA1c in both sleep and physical activity timing. There is more research needed into whether timing of physical activity impacts HbA1c, and more research into the association on whether other sleep factors and HbA1c are significant.

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