Associations of physical activity intensities with markers of insulin sensitivity

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Abstract

Background

Objectively measured physical activity (PA) intensity has traditionally been categorised as light, moderate and vigorous using laboratory calibrated cut-points. The relative contribution of time spent across a spectrum of accelerometer-determined intensities on health outcomes is less clear.

Purpose

To assess the relationship between objectively measured PA intensity on a continuous scale and markers of insulin sensitivity.

Methods

Participants at high risk of type 2 diabetes were recruited from primary care (Leicestershire, UK). PA was measured using an ActiGraph accelerometer. Fasting and post-challenge glucose and insulin levels were assessed using an oral glucose tolerance test. Insulin sensitivity (IS) was calculated using the Matsuda-IS and HOMA-IS indices. Log-linear regression modelling was used to assess the relationship between PA intensity, in 500 count per min (cpm) increments, with markers of IS. Models were controlled for known confounders.

Results

Complete data were available for 569 participants. PA intensity was favourably associated with fasting and 2h insulin and IS, with the association increasing in magnitude with each 500 cpm increment. Differences in HOMA-IS per 10 min of PA ranged from 12.4% (95% confidence intervals 3.7, 21.8%) to 26.8% (11.0, 44.7%) within the moderate-intensity PA category (from 2000-2499 cpm to 3500-3999 cpm). For Matsuda IS, these differences were 22.0% (10.3, 34.9%) and 34.7% (13.9, 59.3%) respectively. Significant associations for

fasting insulin were no longer observed after controlling for BMI, whereas differences associated with 2h insulin and IS were attenuated but still significant.

Conclusion

PA of any intensity may positively influence glucose regulation and insulin sensitivity in individuals at high risk of T2DM in a dose-response manner. Further research is required to identify the intensity thresholds at which clinically relevant benefits occur in this population.

Keywords

Type 2 diabetes; prevention; accelerometer; glucose; insulin

Introduction

The increasing prevalence and associated social and economic burden of type 2 diabetes (T2DM) is widely acknowledged.(43) The predicted impact this is due to have on public resources has made prevention of T2DM a priority nationally and internationally.(35) In England, this has been demonstrated by the launch of the National Health Service (NHS) Diabetes Prevention Programme.(34) A major focus of prevention programmes implemented within routine care pathways is to encourage people to increase their levels of physical activity (PA), improve their diet and lose weight.(11)

Physical activity is a powerful therapeutic agent in the promotion of insulin sensitivity (6) and favourable blood plasma glucose levels.(7) Evidence ranging from epidemiological data to randomised control trials consistently demonstrate strong associations of moderate to vigorous physical activity (MVPA) with cardiovascular health and glycaemic control in individuals with T2DM.(2, 7) The globally accepted recommendation that all adults should engage in 150 minutes of moderate-intensity PA (MPA) or 75 minutes of vigorous-intensity PA (VPA) per week is therefore encouraged in people with and at high risk of T2DM.(8)

Progression of objective measures of activity monitoring technology has facilitated research into PA programmes encompassing the entire intensity spectrum; from replacing sedentary time with light-intensity PA (LPA) (21), to investigation of the minimum volume of maximal intensity PA required to improve health. However, accelerometer measured PA intensity has generally been presented using population dependent counts-per-epoch cut-points categorised as sedentary, light, moderate or vigorous physical activity, with MPA and VPA usually combined and analysed as MVPA. These cut-points have been caibrated against energy expenditure, confirming their "constuct validity", but the "external validity" such as the dose-response relationship between incremental accelerometer measured PA intensity in counts per minute and health outcomes has been less rigorously tested.

The aim of this study was therefore to determine the association of time spent in objectively assessed incremental PA intensities with markers of insulin sensitivity; a precursor to T2DM, in free-living environments in individuals at high risk of T2DM. We hypothesised that above the MPA cut-point (~2000 counts per minute; cpm) there would be a linear increase in the strength of the association between PA intensity and markers of insulin sensitivity up to a threshold above which no further benefit of increasing intensity would be observed.

Methods

This study reports a cross-sectional analysis of baseline data from the Walking Away from type 2 diabetes randomised control trial (RCT), the methods for which have been published previously.(41)

Participants

Participants (N = 833) were recruited from 10 primary care practices in Leicestershire, UK during 2010-2011. Individuals who were identified as being at high risk (individuals scoring within the 90th percentile within each practice) of dysglycaemia; impaired glucose tolerance (IGT; 2h glucose ≥7.8 and <11.1 mmol·L^{-1}) and/or impaired fasting glycaemia (IGF; fasting glucose ≥6.1 and <7.0 mmol·L^{-1}) or undiagnosed T2DM, using the Leicester Practice Risk Score (LPRS) were invited to take part. The LPRS has been shown to have good reliability in predicting prevalence of dysglycaemia (15, 17) and includes questions about anthropometry, ethnicity, family history and antihypertensive therapy; each weighted based on epidemiological evidence. Participants were unaware of their diabetes risk before entering into the study and were excluded if they had known T2DM or were unable to take part in any walking activity. Baseline measurements were performed before treatment allocation by trained staff, who were blinded to study outcomes and followed standard operating procedures. Following this, practices were randomly assigned to either a control or intervention arm. Participants in the control practices were given a lifestyle advice leaflet and

participants in the intervention practices were invited to take part in a pragmatic evidence-based structured education programme designed to promote PA and a healthy lifestyle. The programme involves attendance at a three hour group education session. The primary aim is to promote walking activity by targeting perceptions and knowledge of dysglycaemia and PA self-efficacy as well as facilitating self-regulation such as goal setting, self-monitoring (using pedometers) and relapse prevention. All participants provided written informed consent and ethical approval was obtained from a local NHS research ethics committee.

Objective measurement of physical activity

Participants were instructed to wear a waist-worn accelerometer (Actigraph GT3X, Pensacola, FL, USA) for seven consecutive days, removing for water-based activities and non-waking hours. Data were recorded in 15 second epochs and re-integrated into 60 second epoch files for this analysis. Activity intensity was generated in 500 cpm increments from 0 to 4499 cpm. Any counts recorded above 4500 cpm were grouped together to account for a lack of power at intensities above this. Using a regression equation from a similar population,(Hall) we estimated the number of METs the mid-point of these increments equated to (Table 1).

EE = METs = $(60(3.28 \times 0.0009cpm))/BW$ adapted from (16)

Where BW is body weight (kg) and EE is energy expenditure ($kCal \cdot h^{-1} \cdot kg^{-1}$).

The number of minutes spent within each intensity band per day was calculated. For a day to be considered valid, at least 600 minutes of wear-time had to be recorded; non-wear time was defined as more than 60 minutes of continuous zero counts.(12) All accelerometer-derived variables were computed by summing the values over all valid days and calculating the mean value per valid day. Data were analysed using a commercially available software package (KineSoft V3.3.76, Kinesoft, NewBrunswick, Canada; www.kinesoft.org).

Demographic, anthropometric and biochemical

On the participants' first visit, information regarding ethnicity, smoking status and antihypertensive medication were collected by a health care professional. Body weight (Tanita TBE 611, Tanita, West Drayton, UK), waist circumference (midway between the lower costal margin and the iliac crest) and height were measured to the nearest 0.1kg and 0.5cm respectively.

A standard oral glucose tolerance test using a 75g glucose load was administered to all participants. Individuals were asked to avoid caffeine and strenuous exercise in the preceding 24 hours and to consume only water from 10pm the evening prior to their visit. Fasting and 2 hour post-challenge plasma glucose samples were measured using the glucose oxidase method (Beckman Auto Analyzer, Beckman, High Wycombe, UK) at the Leicester Royal Infirmary. Plasma samples were frozen at -80^{o}C and analysed for fasting and 2 hour insulin at the end of baseline data collection using enzyme linked immune-assay (80-INSHU-E01.1, Alpco Diagnostics 26G Keewaydin Drive, Salen, NH 0.079, USA) within a specialist laboratory (Unilever R&D, Bedfordshire, UK). Analysis was conducted by individuals blinded to the patient's identity and using stable methodologies, standardised to external quality assurance values.

Measures of insulin sensitivity

The homeostatic model assessment of insulin sensitivity (HOMA-IS) and Matsuda indices were used to estimate insulin sensitivity: (29, 32)

HOMA-IS =1/HOMA-IR = $22.5/(G_0 \cdot I_0)$

Matsuda ISI = $10{,}000/\sqrt{G_0 \cdot I_0 \cdot G_{120} \cdot I_{120}}$

Where G_0 is fasting plasma glucose, I_0 is fasting plasma insulin, G_{120} is 2 hour glucose and I_{120} is 2 hour insulin. These models have been shown to correlate reasonably with gold-

standard measures of IS.(33) Matsuda ISI is more likely to reflect factors related to insulin release and peripheral insulin resistance whereas HOMA-IS may be a better measure of hepatic insulin resistance.(19)

Data inclusion

Individuals at high risk of or with dysglycaemia or previously unknown T2DM, a minimum of four valid days of accelerometer data and fasting glucose and insulin data to allow for an assessment of HOMA-IS were included.(30) Valid accelerometer data were available for 727 (87%) participants. Cessation of bleeding or insufficient plasma volumes for the fasting insulin analysis meant that 569 (68%) participants met the inclusion criteria. Of these individuals, 508 (61%) participants also had complete 2 hour glucose and 2 hour insulin results. The number of participants included and excluded can be found in supplemental digital content 1, Figure. Those who were excluded from the HOMA-IS analysis (N = 178) tended to be younger (61.7 years for missing vs. 63.8 $p<0.001$) and more likely to be female (42% vs. 34%; $p = 0.021$). However, there was no difference in BMI, fasting or 2 hour glucose.

Statistical Analysis

Data were analysed using Stata V.14 (StataCorp. 2015, Stata Statistical Software release 14. College Station, TX 77845, USA).

Log-linear regression was used to assess the association of PA intensity with fasting and 2h glucose and insulin levels, and insulin sensitivity.(3) Dependent variables were log transformed as they displayed non-parametric distributions. Time spent in each of the PA intensity increments were entered into models separately due to the correlation between groupings. Sensitivity analyses assessed whether the associations were dependent on the diagnosis of IGR, sex or age (<75 or ≥ 75). Adjustment was not made for multiple

comparisons, therefore data were viewed with caution and in relation to the overall pattern of results. Model one was adjusted for age, sex, ethnicity, smoking status, beta-blocker medication and accelerometer wear time. In order to examine the extent to which adiposity may attenuate these relationships, further adjustment for BMI was made in model two. Data were not adjusted for overall physical activity volume (counts per day) due to collinearity (Supplemental digital content 2, Table). Coefficients were back transformed and represent the factor by which the outcome is multiplied by (95% confidence interval; CI) for a given unit of time spent at each intensity. Data in the text is presented as the percentage difference (95% CI) in the strength of the association between 10 minutes of PA and the outcome.

Results

Characteristics of participants included in the analysis are displayed in *Table 2*.

Physical activity

Time spent in each 500 cpm intensity banding is shown in Figure 1 and supplemental digital content 1, Table. Physical activity intensity ranged from 0-6000 cpm. Total physical activity volume (counts per day) tended to be correlated more strongly with time spent between 1000-3000 cpm, (supplemental digital content 2, Table), indicating most activity was undertaken at the lower end of the MPA range.

Biochemical outcomes

The regression coefficients (95% CI) presented here and used to generate *Figure 2* are displayed in Supplemental digital content 3, Table.

Fasting and 2h glucose

Physical activity intensity was not associated with fasting glucose levels *(Figure 2a & b)*. Time spent in PA intensities less than 500 cpm were associated with higher 2 hour glucose levels (0.91%; 0.49, 1.33%). Time spent in PA at intensities between 500-2499 cpm was associated with a linear change in the strength of the association with 2 hour glucose *(Figure 2c)*. After this level there was no clear increase in the strength of association, although the error around each regression coefficient increased. This relationship was attenuated slightly after adjusting for BMI, with associations observed up to 1999 cpm (-3.98%; -7.79, -0.01%; *Figure 2d*).

Fasting and 2h insulin

Every 10 minutes spent at intensities lower than 500 cpm were associated with 1.66% (0.86, 2.47%) higher fasting insulin levels. Time spent in intensities of 500 cpm and above were associated with lower fasting insulin for each 500 cpm increment up to 3999 cpm, ranging

from -2.67% (-4.46, -0.85%) to -20.47 (-29.84, -7.60%) per 10 minutes of PA. Above this, the difference in the association remained similar *(Figure 2e).* Adjusting for BMI largely attenuated the results (*Figure 2f*).

Time spent in PA intensities below 500 cpm were associated with 2.96% (1.80, 4.14%) higher 2 hour insulin levels per 10 minutes of PA, an association also observed after controlling for BMI (2.61%; 1.41, 3.82%). Per 10 minutes of PA spent in each 500 cpm increment in PA intensity between 500-3999 cpm, the difference in 2 hour insulin changed from -5.00% (-7.52, -2.42%) to -20.75% (-33.93, -4.95%; *Figure 2g*). The time spent in intensities of 4000 cpm and above were still significantly associated with 2 hour insulin levels, but there was no further rise in the strength of the association. The relationship when controlling for BMI was attenuated but still significant and followed a similar pattern *(Figure 2h).*

Insulin Sensitivity

The time spent below 500 cpm PA intensity was associated with lower scores of both HOMA and Matsuda measures of insulin sensitivity *(Figure 2i & k).* Times spent in PA intensities of 500 cpm and above were linearly associated with differences in HOMA-IS from 2.64% (0.64, 4.68%) to 26.75% (10.99, 44.74%) per 10 minutes of PA up to 3999 cpm. Similarly, differences in the association with Matsuda ISI ranged from 5.32% (2.76, 7.94%) to 34.66% (13.85, 59.26%) per 10 minutes of PA. Associations with time spent in intensities above 4000 cpm were statistically significant but of a smaller magnitude than those between 3000-3999 cpm.

After controlling for BMI, associations with HOMA-IR were largely attenuated *(Figure 2j).* However, the relationship with Matsuda was maintained with differences between 500-999

cpm and 3500-3999 cpm 3.91% (1.38, 6.50%) and 23.02% (4.05, 45.46%) respectively *(Figure 2l).*

Sensitivity Analyses

Subgroup analysis revealed that there were no differences in any of the outcomes when the data were stratified by IGR status, except for the relationship between PA intensities between 500-999cpm and fasting glucose (p=0.037). This analysis indicated that the relationship between PA and fasting glucose was stronger in those with IGR with fasting glucose levels 0.7% (0.1, 1.2%) lower per 10mins of PA than those with normal glucose tolerance; 0.1% (0.0, 0.3%) There were no sex or age by intensity interactions.

Discussion

In this cohort of individuals identified as being at high risk of IGR or with undiagnosed T2DM, time spent in 500 cpm increments in objectively assessed PA intensity were linearly associated with lower levels of fasting and 2 hour insulin and 2 hour glucose and higher scores of indexes of insulin sensitivity. Differences in insulin sensitivity per 10 minutes of PA time increased sharply when moving up in 500 cpm bands from 500 cpm to 3999 cpm (roughly equivalent to walking speeds of 1-3.5km·h^{-1};(16)); for example, 10 minutes of PA between 500-999 cpm (up to approximately 1.5km·h^{-1}; (16))was associated with a 5.32% difference in insulin sensitivity (Matsuda ISI) whereas 10 minutes spent between 3500 to 3999 cpm (approximately 3-3.5km·h^{-1})was associated with a 34.66% difference in insulin sensitivity. There did not appear to be any additional change in the strength of the association for time spent at intensities higher than 4000 cpm (3.5km·h^{-1} and above). Results for 2 hour glucose and 2 hour insulin and Matsuda ISI remained largely unchanged after adjustment for BMI whereas fasting measures were attenuated. Based on the accelerometer cut-points validated by Freedson et al. (13), our results suggest that, in individuals at risk of or with dysglycaemia, both LPA and MPA are sufficient to gain improvements in insulin sensitivity; the strength of which is proportional to time spent in PA intensities up to 3999 cpm, above which no further strength in the association was gained.

It has long been accepted that there is a dose-response relationship between PA volume (broadly defined as intensity x duration) and health up to a certain level, with the greatest benefits occurring when moving from a sedentary inactive lifestyle.(1) Showing that the strength of association between time spent in PA and insulin sensitivity increases proportionally to the level of intensity up to a point, is consistent with this theory. Interestingly, we found no additional benefit in this cohort for time spent above 4000 cpm, which equates to approximately 4.7 METs;(16)). This is in contrast to studies that that have shown additional benefits of performing VPA compared to MPA on markers of insulin sensitivity.(23, 25) Our observation that there was no additional benefit in performing PA at the upper end of the MPA range could be attributed to a lack of power in these

intensity bands resulting from the progressively smaller amount of time spent in each intensity increment. However, results from the Cardiovascular Health Study (37) which indicate that increasing habitual walking speed reduces the risk of cardiovascular disease more than increasing distance, suggests that even small increases in PA intensity may translate to long-term longevity. At the lower-intensity end, a number of cross-sectional analyses have shown that replacing sedentary time with LPA is associated with more favourable levels of insulin sensitivity in individuals at high risk of T2DM, who tend to spend long periods of time in sedentary behaviours.(22, 42) These observations have been supported with controlled interventions which have demonstrated that breaking sitting time with short bouts of LPA, and standing, produces benefits in glucose regulation and insulin sensitivity.(21, 38) Results from training intervention studies have been more equivocal with some demonstrating that low-intensity exercise training leads to reductions in HOMA insulin resistance,(27) whereas others have not.(18, 36)

When comparing the intensity at which benefits occurred in the current study to accelerometer cut-points from calibration studies, it appears that for an older population at high risk of T2DM, benefits occur at intensities substantially below the threshold traditionally used to define MVPA. These cut-points, developed for ActiGraph accelerometers by Freedson et al.,(13) are widely used and have been well validated.(20) They are based on calibration with oxygen consumption during treadmill walking/running and equate to 1.5, 3 and 6 METs for LPA, MPA and VPA respectively. Frequently used cut-points are set at <100 cpm for sedentary behaviour, (31) 1952-5724 cpm for MPA and ≥5725 cpm for VPA. Virtually none of the participants from our cohort, who were on average 40 years older than those who were used to calibrate these cut points, performed PA at more than 5725 cpm and differences in insulin sensitivity per 10 minutes of activity within the MPA range (1952-5724cpm) varied from 12.37-26.74% and 21.98-34.66% for HOMA and Matsuda respectively. This indicates that large differences in health outcomes could be expected from participation within the moderate range. In line with this, accelerometer cut-points specifically for older individuals, which may reflect more accurately associations between PA intensity and

health in this population, have recently been investigated.(14) Narrower cut-point ranges at lower intensities have been proposed. Our results suggest that the lower intensity bands proposed by the Generation 100 study,(44) which are dependent on sex and cardiorespiratory fitness, could be used to more precisely assess PA levels and their associations with health in older people. Indeed, there is growing epidemiological evidence to support the notion that risk of morbidity and mortality decreases significantly in individuals who perform PA at lower intensities and volumes than the guidelines recommend.(24) Importantly, this implies that the lower absolute intensity older individuals are able to attain does not result in diminished benefits.

Regardless of their definition, cut-points for light, moderate and vigorous PA all encompass a wide range of relative and absolute intensity levels. The traditional method of reducing data into time spent in these relatively broad categories removes the ability to more accurately define the dose-response relationship with markers of health. To the best of our knowledge, only one other study to date assesses the relationship between incremental accelerometer count per minute cut-point categories and markers of health rather than using predefined cut-points.(5) We extend the findings of this recent study by quantifying associations between participation in PA and health, as well as bringing together recent findings that reducing sedentary time and increasing LPA is also beneficial. Processing accelerometer data in 500 cpm intensity increments covers the whole range of intensities, enabling identification of the minimum intensity at which benefits occur as well as a quantifiable dose-response relationship; all information that will facilitate the development of more achievable interventions with greater improvements.

There are several well-established mechanisms explaining the link between MVPA and improved metabolic health and insulin sensitivity. Skeletal muscle is the primary tissue responsible for glucose disposal (9) and affects insulin signalling in response to both acute and chronic bouts of PA. Assuming the PA levels observed here reflect regular behaviour patterns, we speculate that the higher the intensity of PA engaged in, the more superior the skeletal muscle adaptations that increase insulin sensitivity and drive lower circulating insulin levels.(26) Even very small amounts

of VPA may be important as they can off-set the deleterious effects sedentary time itself has on insulin action.(10) Recently, mechanisms elucidating how LPA may affect health have also been proposed including stimulation of the contraction-mediated glucose uptake pathway as well as inducements of alterations to the insulin signalling pathway.(4)

A major strength of this study is the objective measurement of PA in a free-living environment which is likely to be a more accurate representation of day-to-day behaviour than would be demonstrated by a self-report tool. The deployment of a widely used device (Actigraph GT3X) means the results are directly comparable to other data sets. In addition, the study population were at high-risk of T2DM and were recruited from primary care. Typically, this is a group that is hard to reach in lifestyle research despite representing the type of population referred to diabetes prevention programmes. We also present a comprehensive selection of diabetes-related biochemical outcomes that were measured using robust laboratory techniques.

Limitations include the cross-sectional nature of the analysis, meaning we are unable to draw causal inferences. Although more accurate than self-report, accelerometers may underestimate overall PA because they are unable to accurately quantify non-step based or weight bearing activities such as swimming or cycling. Moreover, due to individual differences in fitness levels, which were not measured in the original study, performing activity at the same number of counts per minute may reflect different relative intensities within our population.(44) It should also be noted that although statistically significant differences in markers of insulin sensitivity and glucose regulation were observed, how these translate to the prevention and management of T2DM remains unclear. However, it is well established that those with greater insulin sensitivity are less likely to develop T2DM.(28)

In summary, our study provides additional evidence that, while the current guidelines promote optimal health,(40) for older individuals at high risk of T2DM, any PA may be beneficial, but, up to 3999 cpm (roughly the speed of a moderately paced walk; 4.7km.h^{-1}), the higher the intensity, the

greater the potential improvement for a given physical activity duration. The nature of this study does not allow us to confirm a causational effect, nevertheless these data stimulate an interesting line of future research investigating the accelerometer measured intensity at which health outcomes are affected in different populations. As has been strongly advocated in recent years,(39) this could then lead to specific targets being set for specific diseases or risk factors, which may increase participation in those who may benefit most for increasing PA due to having more realistic goals and expectations.

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Conflicts of interest and sources of funding

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Authors' contribution

AR & TY had the original idea for the secondary analysis. CE processed the accelerometry data. CJ performed the statistical analysis and prepared the first draft of the paper. All authors contributed to

the development and writing of the paper, revised for important intellectual content and approved the final manuscript.

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Figure captions

Figure 2. <<Above panel a>>> Model 1 adjusted for age, sex, ethnicity, smoking status and β-blocker medication and accelerometer wear time.

<<Above panel b>>> Model 2 adjusted for age, sex, ethnicity, smoking status and β-blocker medication accelerometer wear time and BMI

a. Association between time spent within each PA intensity and fasting glucose levels (N=569)

b. Association between time spent within each PA intensity and fasting glucose levels (N=569)

c. Association between time spent within each PA intensity and 2h glucose levels (N=567)

d. Association time spent within each between PA intensity and 2h glucose levels (N=567)

e. Association between time spent within each PA intensity and fasting insulin levels (N=569)

f. Association between time spent within each PA intensity and fasting insulin levels (N=569)

g. Association between time spent within each PA intensity and 2h insulin levels (N=508)

h. Association between time spent within each PA intensity and 2h insulin levels (N=508)

i. Association between time spent within each PA intensity and HOMA-IS score (N=569)

j. Association between time spent within each PA intensity and HOMA-IS score (N=569)

k. Association between time spent within each PA intensity and Matsuda ISI score (N=508)

l. Association between PA time spent within each intensity and Matsuda ISI score (N=508)

<<Below panels k & l>>Percentage change in biochemical outcomes associated with a 10 minute increase in time spent in 500cpm bands of PA intensities ranging from 0-≥4500cpm. Coefficients are plotted at the mid-point of the intensity band. Dotted lines represent commonly used accelerometer cut-points for light (100 cpm) and moderate PA (1952 cpm)(15)

Supplementary material

Jelleyman SDC 1, Figure.pdf

Jelleyman SDC 2, Table.pdf

Jelleyman SDC 3, Table.pdf