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Changes in Physical Activity and Sedentary Patterns on Cardiometabolic Outcomes in the Transition to Adolescence: ICAD 2.0

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Key Words: moderate-to-vigorous physical activity; light intensity physical activity; sedentary behavior; longitudinal; LDL-c; triglycerides; youth

Abstract

Objective: To examine the associations of changes in physical activity (PA) and sedentary-patterns with changes in cardiometabolic outcomes from childhood to adolescence.

Study design: Youth from the International Children's Accelerometry Database (n=1,088; 55% girls), aged 8-13 years and followed for ~4 years, were used in this analysis. Hip-mounted accelerometers were used and all PA intensities were expressed as the % of total wear-time. Sedentary time (ST) was separated into time spent in bouts <10min and ≥10min. A composite Z-score for cardiometabolic risk (CMR-score) was computed by summing the standardized values for systolic (SBP) and diastolic blood-pressure (DBP), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), and the inverse high-density lipoprotein cholesterol (HDL-c). Multivariate analyses were performed using adjusted linear regression models.

Results: Increase in ST was unfavorably associated with changes in CMR-score (β=0.021; CI=0.004, 0.037), TG (β=0.003; CI=0.001, 0.005), and DBP (β=0.068; CI=0.009, 0.128). Decrease in moderate-to-vigorous PA was unfavorably associated with changes in LDL-c (β=-0.009; CI=-0.017,-0.001) and TG (β=-0.007; CI=-0.013,-0.001). Increase in ≥10min ST was unfavorably associated with changes in CMR-score (β=0.017; CI=0.004, 0.030), LDL-c (β=0.003; CI=0.000, 0.005), and TG (β=0.003; CI=0.000, 0.004). Decrease in light-intensity PA was unfavorably associated with changes in CMR-score (β=-0.020; CI=-0.040, 0.000).

Conclusion: More PA and less prolonged ST are beneficial for cardiometabolic health in youth transitioning to adolescence.

Abbreviations:

CMR-score: cardiometabolic risk score

DBP: diastolic blood pressure

HDL-c: high-density lipoprotein cholesterol

ICAD: International Children's Accelerometry Database

LDL-c: low-density lipoprotein cholesterol

LIPA: light intensity physical activity

MVPA: moderate-to-vigorous physical activity

SBP: systolic blood pressure

ST: sedentary time

TG: triglycerides

WC: waist circumference

Introduction

The role of PA in overall health is well established [1], with sensor-based PA being inversely associated with cardiometabolic risk in youth. [2] However, evidence assessing the relationship between PA and cardiometabolic outcomes in youth has mostly focused on moderate-to-vigorous PA (MVPA), an important factor contributing to cardiometabolic health of youth. [3] Despite the benefits of MVPA, other intensities of PA may also contribute to cardiometabolic health. For instance, sedentary time (ST) has been unfavorably associated with health outcomes such as body-fat percentage and insulin levels. [4, 5]

Moreover, cross-sectional investigations suggest that the manner in which ST is accumulated may play an important role in the associations with health outcomes, with shorter bouts of ST and more frequent breaks potentially favoring healthier cardiometabolic profiles. [6, 7] Despite several experimental findings suggesting that prolonged sedentary bouts may have a negative impact on cardiometabolic pathways [8], evidence from observational investigations on this topic in youth is sparse, inconclusive, and do not allow for the establishment of causality [9, 10]. Longitudinal investigations are a step forward to establishing causality. [11] The public health recommendation to "sit less, move more" is widespread but understanding how distinct PA intensities and patterns influence cardiometabolic outcomes in youth as they progress from childhood to adolescence is important in order for more effective strategies and recommendations to be made.

Our goal was to longitudinally investigate the relationship of changes in LIPA and MVPA, as well as changes in total ST and time spent in prolonged ST with changes in composite and individual cardiometabolic outcomes in a large multi-center sample of youth transitioning to adolescence.

Methods

The International Children's Accelerometry Database (ICAD; http://www.mrc-epid.cam.ac.uk/research/studies/icad/) is a pooled database covering accelerometer and socio-demographic data from more than 20 studies of 3-18 year-old youth worldwide. More details about ICAD aims, study selection, inclusion criteria, and methods have been previously described. [12]

The European Youth Heart Study (EYHS) assessed 1604 youth aged 8-10-year-old from 1) Odense, Denmark and 2) the island of Madeira, Portugal, between September 1997 and July 2000. Those youth were then invited to participate in the study after approximately 6 years. For the current analyses, we considered the participants that had at least 3 valid days of accelerometer data (including one weekend day) and all cardiometabolic outcomes of interest on both time of first data collection (T1) and follow-up, which yielded a total sample of 272 participants from the EYHS. The EYHS was approved by the local scientific ethics committee (case no. 96/272) and performed in accordance with the Helsinki Declaration.

The Avon Longitudinal Study of Parents and Children (ALSPAC) performed in England included 13978 youth who were born between April 1991 and 31 December 1992. Details on all the cohorts can be found in a previous publication. [13] While the assessment moments in the EYHS were approximately 6 years apart, the ALSPAC collected data every 1–3 years; therefore, we excluded wave 2 from ALSPAC and considered waves 1 and 3, so that similar T1 age and follow-up period would be considered. For the current analyses, 816 participants from ALSPAC were included.

In all studies, participant/parental written informed consent was obtained and consulted with their respective research boards to ensure appropriate ethical approval of data-

sharing. Because the ICAD dataset is an anonymous data source, the Human Subject Committee did not review this pooled analysis (i.e. 2019).

A description of the ICAD demographic variables has been previously described. [12] We used the ICAD 2nd classification system for ethnicity, which differentiates between White, Black, Asian, mixed, and other. For the parents' education level, the ICAD 2nd classification system was also used: 1) up to and including completion of compulsory education; 2) some post-compulsory education or vocational training; 3) completed undergraduate or postgraduate education.

Body height and weight were measured with a stadiometer and a calibrated scale, respectively. [12] Waist circumference (WC) was measured with a metal tape according to the protocol previously described. [12]

Cardiometabolic risk factors included systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting high- and low-density lipoprotein cholesterol (HDL-c and LDL-c), and triglycerides (TG). A full description of blood collection procedures for studies in the ICAD database is available elsewhere. [12] A composite Z-score for cardiometabolic risk (CMR-score) was derived by standardizing and then summing the following continuously distributed markers: SBP, DBP, LDL-c, TG, and inverted fasting HDL-c. The standardizing of these factors was achieved by subtracting the sample mean from the individual mean and then dividing by the SD (of the sample mean). The CMR-score was calculated at T1 and follow-up. A higher score implied higher risk.

All accelerometer data were reprocessed by the ICAD group to ensure consistency across studies and waves according to a standardized harmonization protocol. [12] Accelerometer data were collected using the hip-mounted Actigraph 7164, also known as the CSA and MTI. All individual participant data were re-analyzed using KineSoft version 3.3.20

(KineSoft, Saskatchewan, Canada; http://www.kinesoft.org) and reintegrated to 60sec epochs. Periods of 60min of consecutive zeros were considered as non-wear-time, allowing for 2min of non-zero interruptions. The inclusion criteria for accelerometry data for this report were a valid wear-time of ≥10 hours per day for ≥3 days, including one weekend day at both T1 and follow-up time-points. A data dictionary, which provides a definition of all accelerometer variables in the ICAD database, can be found at http://www.mrc-epid.cam.ac.uk/Research/Studies/.

ICAD provides several cut points to differentiate PA intensities. The following cut points were considered: ST<100 counts/min; 100≤LIPA<2000 counts/min; MVPA≥2000 counts/min. The time in bouts of distinct length spent in different PA intensities (i.e. 1-3, 3-5, 5-10, 10+min) were provided by the ICAD database. The time in these bouts was summed to obtain the total time spent in each activity intensity. Additionally, a period of uninterrupted ST was considered a bout, and bouts of <10min and bouts of ≥10min represented non-prolonged and prolonged ST, respectively.

All statistical analyses were performed using IBM SPSS Statistics (version 25.0, 2012, IBM Company, Chicago IL, USA). Descriptive statistics included means ± standard deviation for all measured variables at both moments. Differences between T1 and follow-up were analyzed using paired-sample t-tests.

For all exposures, the % of total wear-time was calculated [i.e. (exposure in minutes / total wear-time in minutes) * 100]. The change (Δ) in % of total wear-time in a specific behavior was then calculated (follow-up % exposure *minus* T1 % exposure) and used as the independent variable in the regression models in order to account for significant differences in total wear-time between time-points. For all cardiometabolic outcomes and the CMR-score, the change variable (Δ) was calculated (follow-up value *minus* the T1 value) and used

in the regression models. Multiple linear regression models were used to assess the relationship between changes in the exposures (i.e. % of ST, LIPA, MVPA, <10min ST, and ≥10min ST) and changes in the outcomes (i.e. CMR-score, SBP, DBP, HDL-c, LDL-c, and TG), adjusting for T1 age, sex, ethnicity, mother education level, father education level, accelerometer valid days, study, follow-up duration, and the outcome and exposure at T1, to control for the variation in their initial levels. A separate regression model was performed for each exposure/outcome pair.

Interactions for sex or study with exposures and the cardiometabolic outcomes were tested by including in each model the respective variable of interaction (e.g. sex*Δ ST%) and examining the p-value for the association of this variable with the specific outcome (e.g. Δ TG) among all the other exposures. Interaction was checked for each independent model and if $p \geq 0.05$, then no interaction existed. In regression models with SBP or DBP, further adjustment for changes in height was performed. All regression models were checked for linearity, normality, and homoscedasticity and all linear regression assumptions were met. In addition, the variance inflation factor was used to check collinearity. All models had a variance inflation factor <2. Additional regression analyses with similar models were performed in four groups (inactive, moderately inactive, moderately active, and active), stratified based on the quartiles of MVPA to examine the associations within each of these groups. Statistical significance was set at $p<0.05$.

Results

No significant interactions for sex or study with exposures and the cardiometabolic outcomes were observed. Thus, girls and boys from all the three studies were combined in the analyses with sex and study added as covariates in the models. A total of 1088 youth (601

girls), who were primarily of Caucasian ethnicity (92%), were included. Participants were from the ALSPAC-England (N=816; 75%), the EYHS-Denmark (N=196; 18%), and the EYHS-Portugal (N=76; 7%). Table 1 shows the participants' demographics, cardiometabolic outcomes, and accelerometer-derived exposures at T1 and follow-up, and the results for the paired-t tests.

Table 1 here

As presented in Table 1, T1 and follow-up were separated by an average of 4.37 years. All exposures significantly changed over time ($p<0.001$), with youth increasing ST by 118.1 min/day, especially the prolonged ST (>10min ST), with an increase of 133.0 min/day. On the contrary, LIPA was reduced by 84.9 min/day, MVPA by 12.8 min/day, and the non-prolonged ST (<10min ST) decreased 15.0 min/day from childhood to adolescence. At T1 (73%) and on follow-up (64%) of the participants had 6 or more accelerometer valid days.

Table 2 displays the results of linear regression examining the associations between changes in PA and sedentary patterns with changes in CMR-score and individual cardiometabolic outcomes, adjusting for the previously mentioned confounders.

Table 2 here

An increase in total ST over time was associated with unfavorable changes in CMR-score, TG, and DBP, and an increase in >10min ST from T1 to follow-up was related with unfavorable changes in CMR-score, LDL-c, and TG ($p<0.05$). A decrease in MVPA over

time was related with unfavorable changes in LDL-c and TG, and a reduction in LIPA from T1 to follow-up was associated with unfavorable changes in CMR-score ($p<0.05$).

Table 3 presents the results for the regression analyses performed for the 4 categories (inactive, moderately inactive, moderately active, and active) based on MVPA quartiles.

Table 3 here

An increase in total ST over time was associated with unfavorable changes in CMR-score, TG, and DBP for the moderately active group at T1. An increase in >10min ST from T1 to follow-up was related with unfavorable changes in TG and DBP for the moderately active group at T1, and with unfavorable changes in CMR-score and LDL-c for the active group at T1 ($p<0.05$). A decrease in MVPA over time was related with unfavorable changes in LDL-c in the inactive group only ($p<0.05$). A reduction in LIPA from T1 to follow-up was associated with unfavorable changes in CMR-score for the moderately inactive ($p<0.05$), and with unfavorable changes in TG and DBP for the moderately active group ($p<0.05$). Finally, a decrease in <10min ST from T1 to follow-up was related with unfavorable changes in TG for the moderately active group and with unfavorable changes in LDL-c for the active group ($p<0.05$).

Discussion

Few investigations have assessed the longitudinal associations of sensor-based PA and ST with cardiometabolic outcomes in youth, [11, 14-16] and most of these investigations had a follow-up of less than 2 years. [17] One investigation longitudinally considered the issue of distinct ST accumulation patterns, but with a follow-up time of 10 months. [11] Thus, our

findings extend the ones from this publication, by encompassing a 4-year follow-up in youth transitioning to adolescence.

Similar to our results, Chinapaw and colleagues found that a decrease in MVPA was unfavorably associated with changes in TG, however in opposition to their findings, [11] MVPA was not related with a CMR-score in our investigation. These differences may be explained by the greater heterogeneity in our sample due to the fact that we used data from 3 countries while Chinapaw and colleagues used data from one country. Most likely, though, discrepancies in the results were due to the fact that they included insulin resistance in their CMR-score. Thus, the components of CMR-score in our investigation may not fully represent the cardiometabolic health risk. Ideally, we would have also considered WC as one of the main outcomes in the analyses, however due to the low number of participants with data on WC at T1 we did not include this marker in the analyses in order to maximize our sample size.

During adolescence, MVPA declines [18] with prolonged ST. [19] A recent review showed that MVPA starts to decline from around the age of primary school entry. [20] Our data confirm this trend with a reduction of approximately 20% (i.e. 12.8 min/day) in MVPA from T1 to follow-up. Previous investigations have observed that MVPA attenuated or eliminated the association between ST and cardiometabolic outcomes in youth. [10, 21, 22] Consistent with most of the existing evidence, [14, 16, 17] we also found that a decrease in MVPA was unfavorably associated with changes in LDL-c and TG, which further demonstrates the importance of increasing or at least maintaining MVPA levels when transitioning from childhood into adolescence. Interestingly, when the regression analyses were stratified by the initial level of MVPA (i.e. inactive, moderately inactive, moderately active, and active), the associations for the decrease in MVPA with unfavorable changes in TG disappeared, which can be explained by the lower sample size in each group, and the unfavorable relationship with changes in

LDL-c was only significant for the inactive group at T1. This finding suggest that reductions in MVPA over time can possibly be deleterious exclusively for the ones already presenting lower MVPA levels.

Cross-sectional data [7, 9, 23] suggest that the pattern of ST accumulation may be differently associated with cardiometabolic outcomes. Extending these cross-sectional findings, we observed that an increase in ≥10min ST was unfavorably associated with changes in CMR-score, LDL-c, and TG, while no relationship was found for the bouts <10min ST in the overall sample. A previous investigation by Chinapaw and colleagues found an increase in prolonged ST (i.e. ≥ 10min) to be favorably associated with changes in CMR-score, [11] thus contradicting our results. However, the study by Chinapaw et al. included different cardiometabolic risk factors into their CMR-score (i.e. triglycerides, total cholesterol/HDL cholesterol ratio, homoeostatic model assessment of insulin resistance, systolic blood pressure, and WC), which may explain the differences between our findings and the ones from this investigation. [11]

Other longitudinal investigations have reported that total ST is unrelated with cardiometabolic outcomes, [15, 17, 24] but these investigations have considered shorter follow-up periods compared to the 4-year follow-up in our investigation. A recent review of longitudinal investigations on this topic considered a follow-up of <2years as an exclusion criteria. [25] In fact, if the magnitude of increase in ST (i.e. 28.2 min/day) observed in a previous investigation with 1-year follow-up [15, 17, 24] is extrapolated to reflect a 4-year follow-up period, the increase in ST (i.e. 112.8 min/day) would be very similar to the increase in ST observed in our study (118.1 min/day). Thus, the differences in the findings for the longitudinal associations of ST patterns with cardiometabolic outcomes between our and prior investigations may simply be due to the follow-up period.

Furthermore, with one exception, [11] previous investigations did not account for specific ST accumulation patterns, such as differentiating between shorter and longer bouts of ST, which are important features considering that the manner in which ST is accumulated may influence the association with health outcomes. [6, 7] Vaisto and colleagues found unfavorable longitudinal associations of total ST with individual cardiometabolic outcomes, [14] whereas our results suggest that mostly prolonged bouts of ST are detrimentally associated with cardiometabolic outcomes in youth. This may be explained by non-prolonged ST bouts being likely associated with higher levels of PA. There is evidence showing that breaks in ST are as much a metric of frequency of PA as that of ST [26], and a higher time spent in non-prolonged ST bouts suggests a higher frequency of ST breaks, and, therefore, potentially higher PA, especially LIPA. There are other metrics that better represent the extent to which ST is prolonged or interrupted (i.e. fragmentation index), [27] but due to the ICAD data we were not able to use this kind of approach.

We found an unfavorable association between a decrease in LIPA and change in CMR-score. Investigations using linear regression models showed that LIPA may be associated with favorable cardiometabolic outcomes, suggesting that LIPA may be an effective substitute for ST when aiming to improve cardiometabolic health. [7, 28] However, these linear regression models may not work with "intermediate intensities" due to collinearity issues, and different statistical approaches have shown no relationship for LIPA with cardiometabolic outcomes. [29, 30] In fact, no associations for the change in LIPA with changes in individual cardiometabolic outcomes were found in our investigation for the overall sample ($p \geq 0.05$), thus the impact of possibly displacing ST with LIPA may not be as effective on improving cardiometabolic outcomes compared to displacing ST with MVPA in the long term. [14]

The small effect-sizes and the lack of a clear explanatory mechanism to explain the different findings observed for overall ST and prolonged ST when considering the distinct cardiometabolic risk factors, justifies future research to better understand if these results can be replicated in other samples or if they are a result of statistical chance. Future longitudinal investigations should take into account that different activity levels at the beginning of the follow-up period can modify the relationship between changes in some of these sensor-based features with the individual cardiometabolic risk factors over time.

Even though our sample consisted of multicenter-data, the majority of participants were Caucasian (92%) and from the ALSPAC, which limits the generalizability to other populations. Another factor that must be presented as a limitation is the age of the data. There is evidence suggesting that the inverse associations for MVPA with overall cardiometabolic risk and dyslipidemia, and the positive association for ST with overall cardiometabolic risk are explained by alterations in body fat content. [31] We did not include a measure of body fat, as WC was only available for a reduced number of participants, and thus this must be recognized as a limitation.

The use of relatively long epochs (60sec) may have limited our ability to detect the relatively common intermittent bouts of PA among youth, thus possibly underestimating youth's MVPA. Youth, especially the ones from younger ages, perform quick and spontaneous changes in the intensity of their movement when they are playing. This means that if we choose a 60sec epoch, we will have an average count value for the entire minute (e.g. LIPA), that can either reflect a situation in which the 60sec were actually spent in LIPA or erroneously another possible scenario in which 10sec were spent in MVPA followed by 40sec of ST, and 10sec more of MVPA (e.g. playing soccer). In our investigation, by using a 60sec epoch, we might have underestimated MVPA while overestimating LIPA to a greater extent in T1 than at the 4-years follow-up when the children were adolescents and potentially

had a less spontaneous PA profile. Consequently, the real differences in MVPA over time could have been higher than the ones found, which could have further strengthened the associations between the decrease in MVPA and the unfavorable changes in cardiometabolic risk factors.

In opposition, the allowance of 2 minutes of non-zero interruptions in the non-wear time criteria could potentially underestimate total ST. When using accelerometer-based data, it is important to account for the type of activities performed during the non-wear time periods. However, we are not dealing with original data, but instead data that came from a large repository in which some criteria (i.e. specified in the methods) were used in order to standardize the data. We were not provided with the information on what the participants were doing in the non-wear time; thus, we could not account for this. Finally, with the 60 minutes of zeros to define non-wear time, we should acknowledge that it makes a difference whether youth took off the accelerometer 1 hour before bedtime or 1 hour during a swimming class. However, all these limitations are constraints of using ICAD data. Beyond the limitations associated with accelerometry, a measure of maturational status was not available to control for the potential confounding effect of maturation changes on cardiometabolic outcomes. Thus, although we controlled for age, it is well known that during the pubertal years there is large heterogeneity in youth of the same age in terms of biological maturation.[32]

Lastly, the ICAD database does not include sleep data. Thus, we were unable to assess all the domains of the 24 hour activity model (i.e. sleep, ST, LIPA, and MVPA) using compositional analysis, which would have allowed us to understand the impact of changing one behavior while taking into account all the other behaviors.

Our results highlight the importance of encouraging MVPA and reducing prolonged ST as a means of improving cardiometabolic outcomes in youth during the transition into

adolescence. Also, our data highlighted the importance of the initial activity level of youth, suggesting that distinct activity profiles may alter the potential for some behavioral domains to change the cardiometabolic risk over time.

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