Association between fatty liver disease markers and physical activity and sedentary time in children and adolescents with obesity

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Abstract

Purpose: To compare patterns of sedentary (SED) time (more sedentary, SED+ vs less sedentary, SED-), moderate to vigorous physical activity (MVPA) time (more active, MVPA+ vs less active, MVPA-) and combinations of behaviors (SED-/MVPA+, SED-/MVPA-, SED+/MVPA+, SED+/MVPA-) regarding nonalcoholic fatty liver diseases (NAFLD) markers.

Methods: This cross-sectional study included 134 subjects (13.4±2.2yrs, body mass index (BMI) 98.9±0.7 percentile, 48.5% females) who underwent 24h/7day accelerometry, anthropometric and biochemical markers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), AST/ALT and Fatty Liver Index (FLI)). A subgroup of 39 patients underwent magnetic resonance imaging-liver fat content (MRI-LFC).

Results: Hepatic health was better in SED- [lower ALT, GGT and MRI-LFC ($p<0.05$), higher AST/ALT ($p<0.01$)] vs SED+ and in MVPA+ [lower ALT ($p<0.05$) and FLI ($p=0.001$), higher AST/ALT ($p<0.01$)] vs MVPA- groups after adjustment for age, gender and Tanner stages. SED-/MVPA+ group had the best hepatic health. SED-/MVPA- group had lower ALT and GGT and higher AST/ALT ($p<0.05$) in comparison with SED+/MVPA+ group independently of BMI. SED time was positively associated with biochemical (high ALT, low AST/ALT ratio) and imaging (high MRI-LFC) markers independently of MVPA. MVPA time was associated with biochemical markers (low ALT, FLI, high AST/ALT) but these associations were no longer significant after adjustment for SED time, except for FLI ($p<0.001$).

Conclusions: Lower SED time is associated with better hepatic health independently of MVPA. Reducing SED time might be a first step in the management of pediatric obesity NAFLD when increasing MVPA is not possible.

What Is Known

- MVPA and SED times are associated with cardiometabolic risks in youths with obesity
- The relationships between NAFLD markers and concomitant MVPA and SED times have not been studied in this population

What Is New

- Low SED time is associated with healthier liver enzymes profiles and LFC independent of MVPA
- While low SED/high MVPA is the more desirable pattern, low SED/low MVPA pattern would have healthier liver enzymes profile compared with high MVPA/high SED, independent of BMI, suggesting that reducing SED time irrespective of MVPA is needed to optimize liver health

Introduction

Pediatric obesity is associated with cardiometabolic diseases (insulin resistance, type 2 diabetes, dyslipidemia, high blood pressure) and nonalcoholic fatty liver diseases (NAFLD) [1, 2]. Defined as an excess of hepatic fat, NAFLD has become the most common liver disease in childhood, regarded as a hepatic manifestation of the metabolic syndrome (MetS) [3]. Youths with obesity and MetS have 5 times the odds of having NAFLD compared with their counterparts with obesity alone, and youths with both obesity and NAFLD have higher insulin resistance, dyslipidemia and blood pressure than youths with obesity alone [4]. As obesity and related cardiovascular and metabolic diseases track into adulthood, there is a need of a life course perspective in pediatric obesity prevention and treatment. Multidisciplinary interventions combining nutritional guidelines and physical activity (PA), particularly moderate to vigorous PA (MVPA), remain the cornerstone therapy of pediatric obesity and related-diseases [3, 5–7]. Behavioral recommendations, that mainly focused on MVPA so far, also advocate now for the minimization of sedentary (SED) time (i.e. waking behavior in a sitting, reclining or lying posture), synergistically with MVPA increase [8]. Both high MVPA and low SED times have been associated with healthier profiles of liver enzymes and reduced liver fat content (LFC) in adults [9–13]. In youths, while evidence supports that increasing MVPA and decreasing SED time reduce cardiometabolic risks [14–17], relationships between accelerometry-based PA levels and NAFLD markers remain understudied [18–20], and only few studies investigated so far the association between SED time and NAFLD surrogate markers (without imaging), showing discrepant results [18, 19, 21]. To our knowledge, no study have measured concomitantly PA and SED times in regard to NAFLD biomarkers and LFC in youths with obesity.

As it remains difficult to implement MVPA in youths with obesity in clinical practice, our team conducted a cross sectional study comparing 7day/24h accelerometry-based patterns of SED (more sedentary, SED+ vs less sedentary, SED-), MVPA (more active, MVPA+ vs less active, MVPA-) and combinations of SED and MVPA times (SED-/MVPA+, SED-/MVPA-, SED+/MVPA+, SED+/MVPA-). Results showed that i) low SED/high MVPA pattern had the most desirable cardiometabolic profile, ii) SED-/MVPA- pattern had lower fat mass, insulin resistance, dyslipidemia and metabolic syndrome risk score, independent of BMI, in comparison with SED+/MVPA+ pattern, and iii) SED time was correlated with cardiometabolic risks independently of MVPA [22, 23]. Considering the strong relationships between cardiometabolic comorbidities and NAFLD [4, 24], it seemed relevant to question whether movement behaviors patterns might be associated with NAFLD markers in the same population.

Therefore, the present study aimed to i) compare patterns of SED, MVPA and combinations of SED and MVPA times regarding liver enzymes (alanine aminotransferase, ALT, as primary criterion) and LFC and ii) investigate correlations between SED time, PA levels and NAFLD markers in children and adolescents with obesity.

Materials And Methods

Participants

This cross-sectional study involved 134 children and adolescents with obesity participating in the betaJUDO study[25]. They were included in 2 centers (Pediatric Obesity Clinic at University Children's Hospital, Uppsala, Sweden, and Paracelsus Medical University, Salzburg, Austria). Inclusion criteria were the followings: (a) 10-17 years old, (b) age-adapted BMI > 30kg.m⁻², (c) medical examination including anthropometric assessment and Tanner's staging, (d) at least 5 valid days out of a possible 7 days of accelerometry measurements, including one of the valid day on a weekend (regardless of PA and SED levels), (e) blood samplings for liver parameters, (f) no contraindication to PA, (g) no additional medical/psychiatric conditions nor medication influencing cardiometabolic, liver or accelerometry data. The study was accepted for Voluntary Harmonisation Procedure (VHP673, VHP2015061) and approved by Ethics Committees and Regulatory Authorities (EudraCT No: 2015-001628-45; EC Sweden: Dnr 2015/279; EC Austria: 415-E/1544/20-2014). Written informed consent were obtained from participants and parents. The trial was conducted according to the Declaration of Helsinki (World Medical Association; Version 2013) and the E6 Guideline for Good Clinical Practice (International Conference on Harmonisation).

Anthropometry and pubertal staging

Standard operating procedures for measurements were harmonized between centers [25]. Weight (kg) was assessed using a standardized calibrated scale (Uppsala: SECA model 704; Salzburg: SECA model 801, Hamburg, Germany). Height (cm) was measured using a stadiometer (Uppsala: Ulmer stadiometer, Busse, Elchingen, Germany; Salzburg: SECA, model 222 stadiometer, Hamburg, Germany). BMI was calculated as weight (kilograms) divided by the square of height (meters). BMI-SDS (Microsoft Excel add-in LMS Growth using WHO growth report Version 2.76) and BMI percentiles (WHO BMI for age) were calculated. Waist circumference (WC, cm) was measured with a flexible tape midway between the superior border of the iliac crest and the lowest rib on a standing patient. Fat mass (FM) percentage was calculated using an InBody S20 bioimpedance device (Biospace, Seoul, Korea) at fasting. Puberty was evaluated with Tanner staging [26, 27].

Biochemical variables

Blood was sampled at fasting. Validation of analyses was performed between laboratories [25]. Serum concentrations of liver enzymes (ALT, aspartate aminotransferase (AST) and gamma-glutamyl transpeptidase (GGT)), total-cholesterol, high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c) and triglycerides (TG) were analyzed by enzymatic photometric analysis. Plasma glucose was analyzed by enzymatic chromatic test. Plasma was used for central analyses of insulin using singleplex enzyme-linked immunosorbent assay kits for each analyte (Mercodia AB, Uppsala, Sweden). Insulin resistance was expressed using homeostasis model assessment of insulin-resistance index (HOMA-IR), $[HOMA-IR] = \text{glycemia} [\text{mmol} \times \text{L}^{-1}] \times \text{insulinemia} [\text{mU} \times \text{L}^{-1}] / 22.5$ [28].

Fatty liver index calculation

Fatty Liver Index (FLI) was calculated as followed:

$$FLI = e^f / (1 + e^f) \times 100$$

$$f = 0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\text{ggt}) +$$

$$0.053 \times \text{WC} - 15.745)$$

$$(\text{TG in mg/dL, GGT in U/L, WC in cm})$$

Although initially developed for adults, FLI is currently used in pediatric clinical trials as a biomarker of steatosis and varies between 0 and 100 [29–31].

Percentage hepatic fat

Percentage hepatic fat was measured by magnetic resonance imaging (MRI) using 1.5 Tesla clinical MRI systems from Philips Medical System (Best, The Netherlands; Uppsala: Philips Achieva system, Salzburg: Philips Ingenia system) [25]. Children were categorized as having hepatic steatosis when percentage hepatic fat $\geq 5\%$ [32].

Physical activity and sedentary time

Movements related behaviors were assessed with the accelerometer Actical® (Philips Respironics, Inc, Murrysville, PA). As previously described [23], it is an omni-directional waterproof device recording accelerations in the range of 0.05–2.0 g, sensitive to movements in the range of 0.35–3.5 Hz, and able to record the magnitude of acceleration and deceleration associated with every movement. The signal was scored as a “count” which was summed over a 1 minute epoch. Participants were asked to wear the device on their non-dominant wrist during 7 consecutive days (24-hours measurements). Non-wear time was defined as ≥ 60 consecutive minutes of zero counts, with allowance for 2 min of counts between zero and 100. Wear time was determined by subtracting non-wear time from 24 hours. A valid day was defined as ≥ 10 h of wear time. Each minute of wear time was classified using established cut points into SED (<1.5 metabolic equivalent of the task, METS), light physical activity (LPA, <3 METS), moderate activity (MPA, 3 to 6 METS) and vigorous activity (VPA, >6 METS) [33]. MVPA was the sum of MPA and VPA. SED+ (more sedentary) and SED- (less sedentary) groups were defined by being respectively upper and under the median of the sample for SB time. MVPA+ (more active) and MVPA- (less active) groups were defined by being respectively upper and under the median of the sample for MVPA time. The 4 combinations (SED-/MVPA+, SED-/MVPA-, SED+/MVPA+, SED+/MVPA-) were created using the median of MVPA for each of SED subsamples.

Statistical Analysis

Statistical analyses were performed using Stata software (version 15, StataCorp, College Station, US). Continuous data were expressed as means and standard-deviations (SD). The normality of the distribution was checked with a Shapiro-Wilk test. Comparisons between groups were performed using Chi-squared or Fisher's exact test for categorical data, and analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test (when the ANOVA assumptions were not met) for continuous variables. Assumption of homoscedasticity was studied using Bartlett's test. When appropriate (omnibus p -value<0.05), post-hoc test for two by two multiple comparison were applied: Tukey-Kramer after ANOVA, Dunn after Kruskal-Wallis test and Marascuilo for categorical data. Relationships between continuous data were explored with Pearson or Spearman correlation coefficient and a Sidak type I error correction. Multivariable analyses were conducted using multiple linear regression in order to compare groups adjusting aforementioned analyses on possible confounders. No specific strategy approach, such as stepwise, was conducted. Covariates were chosen according to univariate results and clinical relevance. Multivariable regression analyses were run with the following covariates: age, gender and Tanner stages (model 2) and age, gender, Tanner stages and BMI (model 3). The normality of residuals was checked and a logarithmic transformation of the dependent variable was performed when appropriate. Differences were considered statistically significant at p <0.05.

Results

One hundred and thirty-four adolescents (mean age 13.4 ± 2.2 yrs, 48.5% females) were included ($n=97$ from Uppsala and $n=37$ from Salzburg). The mean BMI was 98.9 ± 0.7 kg.m⁻². Mean accelerometry wear time was 6.5 ± 1.1 days with 99.4 ± 2.9 percent of daily wear time. All the patients underwent anthropometric measurements, accelerometry and biochemical assessments. A subgroup of thirty-nine patients underwent MRI-LFC measurements. Anthropometrics, accelerometry and hepatic variables for overall sample, SED- and SED+ groups, MVPA- and MVPA+ groups, are presented in Table 1.

Comparison SED+ vs SED- groups and MVPA- vs MVPA+ groups

In univariate analysis (model 1), SED+ group had higher ALT ($p=0.016$), GGT ($p=0.019$), FLI ($p=0.004$) and MRI-LFC ($p=0.012$), with a lower AST/ALT ratio ($p<0.001$) in comparison with SED- group. These results remained significant when adjusted for age, gender and Tanner stages (model 2), except for FLI ($p=0.131$), and when adjusted for age, gender, Tanner stages and BMI (model 3), except for GGT ($p=0.055$). For the three models, the number of subjects with a MRI-LFC $\geq 5\%$ tend to be higher in the SED+ group in comparison to SED- group, without however reaching significance ($p=0.064$, $p=0.056$, and $p=0.067$, respectively) (Table 1).

In univariate analysis (model 1), MVPA- group had higher ALT ($p=0.003$), GGT ($p=0.049$) and FLI ($p<0.001$), with a lower AST/ALT ratio ($p<0.001$) in comparison with MVPA+ group. These results remained significant when adjusted for age, gender and Tanner stages (model 2) and when adjusted for age, gender, Tanner stages and BMI (model 3), except for GGT ($p=0.298$ and $p=0.363$, respectively) (Table 1).

Results regarding insulin resistance and lipid profile have been published elsewhere [22] and are presented in supplementary files for overall sample, SED- and SED+ groups, MVPA- and MVPA+ groups (Supplementary Table 1).

Comparison between SED-/MVPA+, SED-/MVPA-, SED+/ MVPA+ and SED+/MVPA- groups

Anthropometrics, accelerometry and hepatic variables for SED-/MVPA+, SED-/MVPA-, SED+/MVPA+ and SED+/MVPA- groups are presented in Table 2.

SED-/MVPA+ group had a lower MRI-LFC ($p<0.01$) in comparison with the SED+/MVPA- group, and lower ALT ($p<0.01$) and GGT ($p<0.05$) with a higher AST/ALT ratio ($p<0.01$) in comparison with the SED+/MVPA+ and SED+/MVPA- groups, after adjustment with age, gender and Tanner stages.

SED-/MVPA- group had lower SED time ($p<0.001$) but lower MVPA time ($p<0.001$) and higher LPA time ($p<0.001$) in comparison with SED+/MVPA+ group. BMI was not different between the 2 groups ($p=0.108$). However, after adjustment with age, gender and Tanner stages, SED-/MVPA- group had lower ALT ($p<0.05$) and GGT ($p<0.05$) and higher AST/ALT ratio ($p<0.05$), in comparison with SED+/MVPA+ group (Table 2). These results remained significant after adjustment with age, gender, Tanner stages and BMI ($p<0.05$).

Results regarding insulin resistance and lipid profile have been published elsewhere [22] and are presented in supplementary files for SED-/MVPA+, SED-/MVPA-, SED+/ MVPA+ and SED+/MVPA- groups (Supplementary Table 2).

Correlations

All correlations between hepatic variables and accelerometry variables are presented in Fig. 1. SED time was positively correlated with ALT ($p<0.05$), FLI ($p<0.05$) and MRI-LFC ($p<0.01$), and negatively correlated with AST/ALT ratio ($p<0.001$). SED time remained positively correlated with ALT ($p<0.05$) and MRI-LFC ($p<0.05$) and negatively correlated with AST/ALT ratio ($p<0.05$) after adjustment with MVPA time. These associations remained significant after adjustment for age, gender, Tanner stages, BMI and MVPA time ($p<0.05$).

MVPA was negatively correlated with ALT ($p<0.05$) and FLI ($p<0.001$), and positively correlated with AST/ALT ratio ($p<0.001$). MVPA tend to be associated with MRI-LFC, without however reaching significance ($p=0.056$). MVPA remained negatively correlated with FLI ($p<0.001$) after adjustment with SED time.

Discussion

This study aimed to investigate the association between SED and MVPA patterns measured by 24h/7 days accelerometry and NAFLD markers in children and adolescents with obesity. According to our analysis, although SED-/MVPA+ pattern is associated with the best hepatic health surrogates, juveniles with SED-/MVPA- pattern had better biochemical hepatic markers in comparison with those with SED+/MVPA+ pattern, independently of BMI. Moreover, SED time was positively associated with biochemical (high ALT, low AST/ALT ratio) and imaging (high MRI-LFC) markers of hepatic health independently of MVPA.

MVPA time was associated with biochemical markers of hepatic health (low ALT, FLI, high AST/ALT ratio), but these associations were no longer significant after adjustment for SED time (except for FLI). To our knowledge, this is the first study to measure objectively and concomitantly PA and SED times in regard to NAFLD biomarkers and MRI-LFC in youths with obesity. The results demonstrate the importance of a reduced SED time on hepatic health, irrespectively of MVPA, in youths with obesity.

In the subgroup who underwent liver MRI, the proportion of subjects having a LFC $\geq 5\%$ was 46% ($n = 18/39$), which is in keeping with previous studies showing a large variability in NAFLD prevalence in youths with obesity, depending on the diagnostic method [7, 20, 34–36]. In a meta-analysis based on various diagnostic methods (ALT, ultrasonography and MRI), NAFLD prevalence was estimated at 34% in a large sample of 23 892 youths under 14 years old [34]. Studies measuring percentage hepatic fat by MRI estimated a prevalence between 30 and 44% depending on the cut-off points of hepatic fat fraction [20, 35, 36].

The better hepatic health in SED-/MVPA + group is fully in line with the more favorable cardiometabolic health found in youths meeting guidelines for both MVPA and SED times [22, 37, 38]. The present results strengthens a body of evidence promoting PA recommendations in order to optimize liver health in young subjects [18–20, 34, 39]. Moreover, the comparison between SED-/MVPA- and SED+/MVPA + groups and the mutually adjusted model of correlations between movements-related behaviors and NAFLD markers strongly highlights the importance of SED time in determining optimal liver health, independent of MVPA level. This is concordant with previous findings in adults reporting a positive independent association between SED time and LFC [10, 12, 13]. Interestingly, Li et al recently showed in more than 16 000 adults that after adjusting for MVPA, increasing quartiles of SED time were associated with a higher prevalence of elevated ALT and GGT, which remained significant after further adjustment for cardiometabolic traits (including BMI, lipids and HOMA-IR) [9]. In contrast, increasing quartiles of MVPA were associated with a lower prevalence of elevated ALT after adjustment for SED time, but this became non-significant after further adjustment for cardiometabolic traits [9]. In youths, while evidence now supports that decreasing SED time reduces cardiometabolic risks [22, 40–42], only Martins et al previously found a positive association between SED time and ALT [19]. Norman et al however showed that screen time, a main contributor to SED time, was positively associated with cardiometabolic parameters and ALT, independent of MVPA time, in adolescents with obesity [21], suggesting that limiting screen time would represent an independent lever of action to improve hepatic health. All these results are in line with recently proposed anti-obesity strategies aiming at breaking up prolonged periods of SED time in youths, replacing it with MVPA (the preferred and more efficient scenario) or with LPA (beneficial but with lower effect estimates) [43, 43–45]. Winters-van Eekelen recently showed that reallocation of SED time with MVPA was associated with less total, visceral and liver fat in adults [46].

The present results have to be considered in light of some limitations. First, only a subgroup of subjects underwent liver MRI. Although MRI-LFC has been found correlated with SED time, the absence of correlations between MRI-LFC and MVPA might be explained by the small sample size. However, although liver enzymes alone are inadequate for identification of hepatic steatosis in children, ALT remains the best biochemical marker of hepatocellular lipid content [47]. It has been associated with insulin resistance and cardiometabolic health in adolescents [48]. Secondly, as previously discussed [22, 23], while accelerometry is the gold standard method for measuring movements-related behaviors, MVPA has been potentially overestimated at the expense of LPA. While Actical was shown comparable to the Actigraph GT3X in youths [49], Migueles et al. recently demonstrated that MVPA time largely differed across attachment sites (hip vs wrist), acceleration metrics (number of days and hours per day) and cut-points in youths with obesity [50]. These parameters were however similar for all the participants of the present study. The wrist attachment site had been chosen to increase wear compliance [26], which is a strength of the present study, providing measurements with more than 99% of wear time during a mean of 6.5 days. Finally, Swedish children are known to have a meaningful 50% higher MVPA than children of other European countries [51].

While recommendations have largely focused on MVPA so far, the present study reinforces the need to reduce SED time, synergistically with the increase in MVPA time, to optimize liver health in youths with obesity. In clinical practice, youths with obesity should benefit from an individual behavioral diagnostic targeting all movements behaviors, and stakeholders should be sensitized to support the shift from long periods of SED time to daily routines incorporating bouts of PA. Furthermore, reducing SED time might be a first step in the management of pediatric obesity NAFLD when increasing MVPA is not possible. Long-term cohort studies on the impact of changes in PA and SED times on hepatic health outcomes, and interventional studies with a sequential action plan (i.e. sequencing the actions into a first phase with the aim to reduce SED time followed by a classic supervised MVPA training), are needed.

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; FLI: Fatty liver index; GGT: gamma-glutamyl transpeptidase; HDL-c: High density lipoprotein cholesterol; HOMA-IR: Homeostasis model assessment of insulin-resistance; LDL-c: low density lipoprotein cholesterol; LFC: Liver fat content; LPA: Low physical activity; METS: Metabolic equivalent of the task; MPA: Moderate physical activity; MRI: Magnetic resonance imaging; MVPA: Moderate to vigorous physical activity; NAFLD: Nonalcoholic fatty liver disease; PA: Physical activity; SED: Sedentary; TG: triglycerides; VPA: Vigorous physical activity; WC: Waist circumference

Declarations

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Code availability: not applicable

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Compliance with Ethical Standards: The study was accepted for Voluntary Harmonisation Procedure (VHP673, VHP2015061) and approved by Ethics Committees and Regulatory Authorities (EudraCT No: 2015-001628-45; EC Sweden: Dnr 2015/279; EC Austria: 415-E/1544/20-2014). The trial was conducted according to the Declaration of Helsinki (World Medical Association; Version 2013) and the E6 Guideline for Good Clinical Practice (International Conference on Harmonisation).

Consent to participate: Written informed consent were obtained from participants and parents.

Consent for publication: not applicable

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Tables

Table 1: Anthropometric, accelerometry and hepatic variables for overall sample, SED-, SED+, PA+ and PA- groups. Model 1: univariate analysis. Model 2: adjusted with age, gender and Tanner. Model 3: adjusted with age, gender, Tanner and BMI.

	Overall (n = 134)	SED- (n = 67)	SED+ (n = 67)	p-value Model 1	p-value Model 2	p-value Model 3	PA+ (n = 67)	PA- (n = 67)	p-value Model 1	p-value Model 2	p-value Model 3
Anthropometry											
Age (year)	13.4 ± 2.2	13.1 ± 2.3	13.7 ± 1.9	0.093	NA	NA	13.0 ± 2.3	13.8 ± 1.9	0.024	NA	NA
Females (n, %)	65 (48.5)	33 (49)	32 (47)	0.863	NA	NA	33 (49)	32 (47)	0.863	NA	NA
Tanner stage	3.8 ± 1.3	3.7 ± 1.3	3.9 ± 1.3	0.549	NA	NA	3.7 ± 1.3	3.9 ± 1.3	0.747	NA	NA
BMI (kg×m ⁻²)	34.3 ± 5.2	32.9 ± 5.5	35.6 ± 4.5	0.002	0.017	NA	32.6 ± 4.8	36.1 ± 5.0	<0.001	0.006	NA
Z-BMI (z-score)	3.18 ± 0.48	3.19 ± 0.51	3.16 ± 0.45	0.042	0.161	NA	3.14 ± 0.48	3.22 ± 0.48	0.041	0.189	NA
BMI (percentile)	98.9 ± 0.7	98.8 ± 0.8	99.0 ± 0.7	0.015	0.014	NA	98.7 ± 0.8	99.0 ± 0.7	0.011	0.014	NA
WC (cm)	109.0 ± 13.8	105.8 ± 15.1	112.3 ± 11.5	0.012	0.024	0.155	103.7 ± 13.8	114.3 ± 11.7	<0.001	0.001	0.109
FM percentage (%)	44.0 ± 7.3	41.9 ± 6.5	46.1 ± 7.6	0.002	0.011	0.036	42.3 ± 7.0	45.7 ± 7.3	0.015	0.017	0.124
Accelerometry											
Sedentary time (min/day)	640 ± 116	557 ± 38	723 ± 109	<0.001	<0.001	<0.001	584 ± 61	696 ± 171	<0.001	<0.001	<0.001
LPA (min/day)	483 ± 107	533 ± 88	433 ± 103	<0.001	<0.001	<0.001	494 ± 80	473 ± 111	0.401	0.276	0.322
MPA (min/day)	186 ± 76	222 ± 75	149 ± 59	<0.001	<0.001	<0.001	248 ± 50	124 ± 84	0.001	<0.001	<0.001
VPA (min/day)	6 ± 10	8 ± 14	4 ± 5	0.023	0.047	0.145	10 ± 13	2 ± 3	<0.001	<0.001	<0.001
MVPA (min/day)	192 ± 81	231 ± 81	153 ± 61	<0.001	<0.001	<0.001	258 ± 56	127 ± 86	<0.001	<0.001	<0.001
Total PA (min/day)	676 ± 139	764 ± 72	586 ± 135	<0.001	<0.001	<0.001	752 ± 81	599 ± 144	<0.001	<0.001	<0.001
Hepatic variables											
ALT (U/L)	32.8 ± 27	25.3 ± 12	40.3 ± 34.9	0.016	0.014	0.016	27.4 ± 22.8	38.1 ± 29.8	0.003	0.038	0.043
AST (U/L)	28.9 ± 12.7	27.5 ± 8.6	30.4 ± 15.9	0.843	0.561	0.549	27.6 ± 8.7	30.2 ± 15.7	0.608	0.631	0.611
AST/ALT ratio	1.07 ± 0.39	1.18 ± 0.35	0.96 ± 0.05	<0.001	0.004	0.006	1.20 ± 0.39	0.94 ± 0.35	<0.001	0.007	0.009
GGT(U/L)	21.4 ± 14.3	18.2 ± 8.5	24.7 ± 17.8	0.019	0.023	0.055	19.1 ± 12.3	23.7 ± 15.7	0.049	0.298	0.363
FLI	34.2 ± 27.2	28.3 ± 26.0	40.4 ± 27.3	0.004	0.131	NA	23.6 ± 23.3	44.8 ± 26.9	<0.001	0.001	NA
MRI-LFC (%) ^a	6.3 ± 7.2	4.2 ± 2.4	8.0 ± 7.3	0.012	0.010	0.013	4.0 ± 2.4	8.1 ± 9.0	0.054	0.077	0.102
MRI-LFC ≥ 5% (n, %) ^a	18 (46)	5 (29.4)	13 (60.0)	0.064	0.056	0.067	7 (41.2)	11 (50.0)	0.412	0.765	0.989

ALT: alanine aminotransferase; AST: Aspartate aminotransferase; BMI: body mass index; FLI : Fatty Liver Index; FM: fat mass; GGT: gamma-glutamyl transferase; LFC : liver fat content; LPA: light physical activity; MPA: moderate physical activity; MRI: magnetic resonance imaging; MVPA: moderate to vigorous physical activity; NA . no-adjustment; VPA: vigorous physical activity; WC: waist circumference. ^an=39 (n=17 in SED- group, n=22 in SED+ group, n=17 in MVPA+ group and n=22 in MVPA-group)

Table 2: Anthropometric, accelerometry and hepatic variables for SED-/MVPA+, SED-/MVPA-, SED+/PA+ and SED+/MVPA-. P-values are adjusted with age, gender and Tanner.

	SED-/MVPA+ (n = 33)	SED-/MVPA- (n = 34)	SED+/MVPA+ (n = 33)	SED+/MVPA- (n = 34)
Anthropometry and body composition				
Age (year)	12.4 ± 2.3	13.6 ± 2.2	13.1 ± 1.8	14.2 ± 1.9
Females (n, %)	15 (45)	17 (50)	16 (48)	18 (52)
Tanner stage	3.4 ± 1.5	3.9 ± 1.3	3.7 ± 1.3	4.1 ± 1.2
BMI (kg×m ⁻²)	31.3 ± 4.6	34.6 ± 5.9	35.3 ± 4.8	36.0 ± 4.3
Z-BMI (z-score)	3.24 ± 0.54	3.14 ± 0.48	3.18 ± 0.48	3.17 ± 0.43
BMI (percentile)	98.7 ± 0.8	98.8 ± 0.8	98.9 ± 0.7	99.0 ± 0.6/a
WC (cm)	99.9 ± 11.9	111.6 ± 15.9	110.9 ± 12.3	113.6 ± 10.8 *
FM percentage (%)	41.9 ± 6.6	42.0 ± 6.5	46.0 ± 6.9 *#	46.1 ± 7.5 *#
Accelerometry variables				
Sedentary time (min/day)	553 ± 44	562 ± 31	674 ± 50 ***###	769 ± 129 ***###†††
Light PA (min/day)	496 ± 82	570 ± 78	460 ± 59 ###	408 ± 127 **##†
Moderate PA (min/day)	281 ± 46	165 ± 49 ***	197 ± 37 ***##	104 ± 35 ***###†††
Vigorous PA (min/day)	13 ± 18	4 ± 5 **	6 ± 5	2 ± 2 **†††
MVPA (min/day)	294 ± 53	169 ± 51 ***	203 ± 38 ***###	106 ± 36 ***###†††
Total PA (min/day)	790 ± 65	739 ± 71	663 ± 68 *	514 ± 143 ***###†††
Hepatic variables				
ALT (U/L)	23.5 ± 11.9	26.9 ± 12.0	40.5 ± 37.7 *#	40.7 ± 32.5 *#
AST (U/L)	27.3 ± 7.5	27.6 ± 9.6	29.7 ± 10.8	31.1 ± 19.5
AST/ALT ratio	1.27 ± 0.36	1.10 ± 0.32	0.99 ± 0.41 *#	0.93 ± 0.41 *#
GGT (U/L)	17.3 ± 7.0	18.9 ± 9.7	25.4 ± 18.3 *#	25.9 ± 17.5 *#
FLI	18.5 ± 19.3	37.2 ± 28.4	38.8 ± 29.2	41.9 ± 25.8
MRI-LFC (%) ^a	3.81 ± 1.97	4.47 ± 2.25	4.63 ± 2.26	11.24 ± 10.78 **
MRI-LFC ≥ 5% (n, %) ^a	2 (33.3)	3 (27.3)	5 (45.4)	8 (72.7)

ALT: alanine aminotransferase; AST: Aspartate aminotransferase; BMI: body mass index; FLI : Fatty Liver Index, FM: fat mass; GGT: gamma-glutamyl transferase; LFC : liver fat content; LPA: light physical activity; MPA: moderate physical activity; MRI: magnetic resonance imaging; MVPA: moderate to vigorous physical activity; VPA: vigorous physical activity; WC: waist circumference

Different from SED-MVPA+ : *p< 0.05 ; **p<0.01 ; ***p<0.001

Different from SED-MVPA- : #p<0.05 ; ## p<0.01 ,### p<0.001

Different from SED+MVPA+; † p < 0.05 ; †† p<0.01 ; †††; p<0.001

^a n=39 (n=11 in SED-/MVPA+ group, n=6 in SED-/MVPA- group, n=11 in SED+/MVPA+ group and n=11 in SED+/MVPA- group)

Figures

Figure 1

Heatmap representation of correlations between anthropometric, hepatic and accelerometry variables. The darkest is the box, the higher is the correlation. Left: unadjusted model. Right: adjusted for sedentary time when physical activity was modelled as the main exposure and for MVPA when sedentary time was modelled as the main exposure. *p<0.05, **p<0.01, ***p<0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; FLI: fatty liver index; FM: fat mass; GGT: gamma-glutamyl transpeptidase; LFC: liver fat content; LPA: light physical activity; MRI: magnetic resonance imaging; MVPA: moderate to vigorous physical activity; PA: physical activity; SED: sedentary; WC: waist circumference

Supplementary Files

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