Physical activity attenuates metabolic risk of adolescents with overweight or obesity: the ICAD multi-country study

Original Research Article

Physical activity attenuates metabolic risk of adolescents with overweight or obesity: The ICAD Multi-country Study

Running title: Physical activity, obesity and metabolic risk

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ABSTRACT

Background: Although the benefits of physical activity (PA) at an early age are well established, there is no robust evidence of the role of PA as well as its intensities in attenuating the association between weight status and metabolic risk among adolescents. In this investigation, we analyzed the association between weight status, intensities of PA, and metabolic risk among adolescents.

Methods: Data from six cross-sectional studies in the International Children's Accelerometry Database were used (N=5,216 adolescents; boys 14.6 ± 2.1 y and girls 14.7 ± 2.0 y). Weight status was assessed and classified according to body mass index. Fasting glucose, triglycerides, inverse high-density lipoprotein cholesterol, and blood pressure composed the metabolic risk indicator (z-score). PA was measured by accelerometers. The estimated age of peak height velocity was used as a covariate for somatic maturation.

Results: We observed that increase in weight status showed a strong positive relationship with metabolic risk. However, adolescents with overweight or obesity in the highest tertile of PA (moderate-to-vigorous and vigorous intensity) showed a similar metabolic risk score as the normal weight groups. Moderate intensity PA seemed related to metabolic risk even within some categories of vigorous PA.

Conclusions: We conclude that PA attenuates the metabolic risk of adolescents with overweight or obesity. Although this attenuation is largely explained by vigorous PA, moderate intensity seems also important for better metabolic profile.

Key words: exercise; ICAD; metabolic syndrome; cardiovascular risk

INTRODUCTION

The childhood obesity pandemic has changed the profile of chronic disease among children and adolescents [1]. There is increasing attention on the assessment of metabolic risk factors such as homeostatic model assessment of insulin resistance (HOMA-IR), blood pressure, fasting glucose, triglycerides and high-density-lipoprotein cholesterol (HDL-C) during early ages [2,3]. In a comprehensive sample of 4,581 participants of the International Children's Accelerometry Database (ICAD), Kuzik et al. [2] found that 45% of children and adolescents presented with at least one of these metabolic risk factors. Thus, both the prevention and treatment of early risk factors in children and adolescents should be considered as priorities.

Physical activity (PA) is well established as a key determinant in the prevention and treatment of childhood obesity and early metabolic risk factors [2,4]. However, unlike in adults [5,6], the protective effect of PA in attenuating the association between weight status and metabolic risk indicators in youth is unclear. Although PA seems to have a positive influence on inflammatory markers associated with overweight and obesity during adolescence [7], little robust evidence is available in this context. Among the gaps, few studies adopted objective measures of PA, limiting their ability to assess the potential effects of different intensities of PA on metabolic health [2]. Also, maturation plays an important role on metabolic profile especially during adolescence and not accounting for its influence on metabolic markers can confound data interpretation [8,9].

Identifying the role of PA and its specific intensities on metabolic risk indicators for normal weight, but especially for children and adolescents with overweight or obesity, can provide information for future international recommendations and for clinical practice regarding the prevention and treatment of early metabolic risk factors

in early life. Thus, we analyzed the association between weight status, intensities of PA, and metabolic risk among adolescents, with special consideration to the role of PA in attenuating the positive association between obesity and metabolic risk among adolescents.

METHODS

Design

The International Children's Accelerometry Database (ICAD) (http://www.mrc-epid.cam.ac.uk/research/studies/icad) has the aim of pooling data on both cross-sectional and longitudinal PA studies conducted among children and adolescents worldwide. More information about the study process has been previously described elsewhere [10]. Briefly, the dataset has pooled objectively measured ActiGraph accelerometer data (ActiGraph, LLC, Pensacola, Florida). This data set used standardized data reduction techniques on 46,131 raw ActiGraph data files between 2008 and 2010 [10]. Moreover, data of sociodemographic, anthropometric, and cardiometabolic factors were also pooled when available. Participants' age ranged from 3 to 18 years. For the present study, we used data from six cross-sectional studies from five countries: the ALSPAC (England), the EYHS Denmark (Denmark), the EYHS Estonia (Estonia), the EYHS Portugal (Portugal), the NHANES 2003-04 (United States of America), and the NHANES 2005-06 (United States of America).

Sample

The initial sample was composed of 21,667 adolescents with complete accelerometer data: the ALSPAC (n=12,746), the EYHS Denmark (n=2,045), the EYHS Estonia

(n=660), the EYHS Portugal (n=1,356), the NHANES 2003-04 (n=2,372), and the NHANES 2005-06 (n=2,488). Due to missing data on sociodemographic, anthropometry, metabolic variables, as well as invalid accelerometer data, the final (included) sample was composed of 5,216 adolescents (2,730 girls): the ALSPAC (n=1,588), the EYHS Denmark (n=1,452), the EYHS Estonia (n=421), the EYHS Portugal (n=596), the NHANES 2003-04 (n=602), and the NHANES 2005-06 (n=557), with age ranging from 10 to 17 years of age. Ethical approval for all studies were obtained from the local ethics committees, including the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Metabolic risk score

Fasting blood glucose, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured following a fasting period of at least 12 hours using standard clinical procedures previously described, with limited between-study variation [10,11]. Systolic and diastolic blood pressure were measured using manual and automatic methods. As outcome, we created a continuous metabolic risk score, in which, z-scores from the above-mentioned metabolic variables were created according to sex and chronological age (year) [12]. This indicator is widely accepted as an indicator of cardiovascular risk among adolescents [13]. After this, all indicators were summed to create the indicator of metabolic risk score, given that HDL-C was multiplied per -1 (inverse) and mean of blood pressure z-scores ($SBP_{z\text{-}score}$ + $DBP_{z\text{-}score}$ / 2) was included in the sum as shown in the following equation:

Metabolic risk score: ($HDL\text{-}C_{z\text{-}score}$ * -1) + $triglycerides_{z\text{-}score}$ + $fasting\ glucose_{z\text{-}score}$ + ($SBP_{z\text{-}score}$ + $DBP_{z\text{-}score}$ / 2)

Waist circumference was not included in the overall indicator of metabolic risk due to its close association with BMI, which could confound the results. A detailed description of these procedures has been described previously [10,11].

Body mass index

Body mass index (BMI) was used to indicate weight status, using values of stature (expressed as m) and body mass (expressed as kg). The values provided by Cole et al. [14] were used to classify the participants as normal weight, overweight or obese, which include specific cutoff points for each age group and sex.

Physical activity (PA)

Physical activity was collected using different Actigraph accelerometers. The ALSPAC study used the Actigraph models 7164, 71256, GT1M; the EYHS Denmark, Estonia and Portugal study used the Actigraph model 7164; and the NHANES 2003-04 as well as the 2005-06 studies used the Actigraph model GT1M. All studies adopted the placement at the hip protocol. Moreover, the ALSPAC and both NHANES cohorts adopted a protocol of 7 consecutive days of wearing the accelerometer, while the EYHS Denmark, Estonia and Portugal studies adopted the 4 consecutive days (2 weekdays and 2 weekend days) wearing protocol. Aiming to standardize the procedures, ICAD reanalyzed PA data from accelerometers using 60 second epochs. Non-wear time was considered as 60 minutes of consecutive zeros with tolerance of 2 minutes of nonzero epochs. Moreover, aiming to minimize the missing data, we adopted the cutoff point of 500 minutes per day as a valid day of measurement and a minimum of one valid day per week. To classify sedentary time and intensities of PA (moderate [MPA], vigorous

[VPA], and moderate-to-vigorous [MVPA]), we used the cut-points provided by Evenson et al.[15]. A detailed description of how PA measures were pooled has been described previously [10].

Confounders

Chronological age, peak height velocity, cohort, accelerometer wear time and mothers' educational status were adopted as confounders. The age of peak height velocity was estimated using a logarithm that included chronological age and stature provided by Moore et al. [16].

Statistical procedures

Characteristics of the sample were described using means and 95% confidence intervals, which were used to compare characteristics between groups [17]. Linear regression models adjusted by accelerometer wear time, sedentary time, study, chronological age and age at peak height velocity were used to analyze the independent associations between intensities of PA and BMI in predicting metabolic risk. The joint association of weight status and tertiles of PA intensities in predicting metabolic risk score was analyzed by ANCOVA using confidence intervals for differences between groups. All analyzes were conducted in STATA 15.1, adopting statistical significance as $p<0.05$.

RESULTS

From the initial sample (n=21,667), only 5,216 adolescents presented blood variables from six different studies: the ALSPAC (n=1,588), the EYHS Denmark (n=1,452), the EYHS Estonia (n=421), the EYHS Portugal (n=596), the NHANES 2003-04 (n=602),

202 and the NHANES 2005-06 (n=557). Characteristics of the included and excluded
203 sample are presented on **Table 1.** Included participants were relatively older, presented
204 lower physical activity levels and higher sedentary time. However, the proportion of
205 sex, weight status and mother's education were similar between the included and
206 excluded sample.
207
208 Characteristics of the included sample are presented in **Table 2**. Girls presented
209 lower PA levels, younger age of peak height velocity, smaller waist circumference, and
210 lower fasting glucose and systolic blood pressure compared to boys ($p<0.05$). On the
211 other hand, girls had higher BMI, diastolic blood pressure, HDL-C and triglycerides
212 ($p<0.05$).
213
214 **Table 1 about here**
215
216 Joint associations between PA intensities (VPA and MVPA) and BMI in
217 predicting metabolic risk score are presented in **Table 3**. Among the models, both PA
218 and BMI were associated with metabolic risk score. The association between VPA and
219 metabolic risk as well as MVPA and metabolic risk were similar in both sexes.
220 However, the inclusion of PA in the models did not contribute much to the variance in
221 metabolic risk score already explained by BMI.
222
223 **Table 2 about here**
224
225 Metabolic risk score according to tertiles of PA (MVPA and VPA) and BMI
226 status are presented in **Figure 1**. The group of participants with obesity in the first

tertile of both MVPA and VPA presented the most adverse values of metabolic risk. Boys with normal weight in the first tertile of MVPA showed higher metabolic risk compared to their counterparts of the third tertile. The gradual association between mutually exclusive categories of PA/weight status and metabolic risk was clearer for boys, however the third tertile of PA appeared to be a protective factor in both sexes regardless of weight status. Moreover, girls with overweight in the second tertile of PA showed similar metabolic risk of their counterparts with normal weight.

Figure 1 about here

The association of MPA and body mass index with metabolic risk score according to weight status and tertiles of VPA is presented in **Table 4**. Body mass index was significantly associated with metabolic risk score among all weight status and tertiles of VPA. MPA was associated with metabolic risk in the tertiles one and three of VPA among boys, as well as in the intermediary tertile among girls.

Table 3 about here

DISCUSSION

Our main finding was that a lower metabolic risk in adolescents with overweight and obese in the highest tertiles of PA was similar to the metabolic risk of their counterparts with normal weight. We also observed that VPA seemed to be strongly associated with this modelling effect. Moderate PA also explained variations in metabolic risk, reinforcing international guidelines, which suggest 150 min/week of MVPA for health.

To our knowledge, this is the first study that analyzed this association and the plausible attenuation effect of PA on metabolic risk using a comprehensive sample with device-based monitoring of PA.

Overweight and obesity are associated with several negative health outcomes even among adolescents, including cardiovascular diseases [2,18]. Several mechanisms may explain the positive association observed between BMI and metabolic risk. Excess adipose tissue, that often goes along with increased BMI, results in the increased secretion of free fatty acids [19], reduction of adiponectin [20], an increase of inflammatory markers such as IL-6 and CRP [7], and an increase in insulin resistance, all of which contribute to the hyperlipidemia, hypertension, and glucose intolerance components of the metabolic syndrome [21]. PA, on the contrary, is associated with a reduced metabolic risk [11] through the reduction of inflammatory factors [7] and reduction of adiposity [22].

Our results suggest that, overweight/obesity are associated with metabolic risk among adolescents, but PA is capable to attenuate this association. Adolescents with overweight and obesity, in the highest tertile of PA showed reduced metabolic risk compared to counterparts with normal weight. A previous investigation from the ICAD database found that MVPA was only positively associated with metabolic risk (presence of at least one metabolic risk factor) among children and adolescents with normal weight [2], which is somewhat distinct from our findings. This difference may be explained by differences in the analytical procedures used (categorical vs continuous outcomes) and by differences in the age range of participants included (children + adolescents vs adolescents only). In addition, we opted to adjust the analyses for biological maturation, which is an important factor to be considered for both PA and

276 cardiovascular risk in this age group (adolescence) [8,9]. Thus, it is possible that PA
277 provides more benefit for groups with overweight and obese with advancing age.

278 The observed risk attenuation by PA was clearer for boys. This result can be
279 explained in part by the lower level of general PA [23] and VPA among girls with
280 overweight or obese compared to boys, potentially due to the effects of obesity on
281 motor competence and difficulty with movement of their higher body mass [24,25].
282 Here, for example, girls in the third tertile showed significantly less MVPA (girls: ~67
283 min/day vs boys: ~94 min/day) and VPA (girls: ~23 min/day vs boys: ~36 min/day)
284 than boys. This also suggests that higher amounts of PA are needed for metabolic risk
285 attenuation among adolescents with overweight and obesity.

286 Interestingly, we observed similar results when we compared models with
287 MVPA and VPA. Although there is clear evidence that more intense PA provides
288 additional benefits for health [26], our findings suggests that even MPA seems
289 important for a better metabolic profile. This may have a special practical implication,
290 as adolescents, especially those who are overweight and obese, are more likely to take
291 part in and adhere to PA programs of lighter intensity (i.e. MPA instead of VPA) [27].

292 The potential attenuation effect of PA in the association between weight status
293 and metabolic risk can occur through different mechanisms. Both PA and obesity
294 present convergent mechanisms to metabolic risk factors such as inflammation [7]. PA
295 is associated with a reduction of inflammatory factors, while obesity is associated with
296 increased inflammatory factors. Moreover, PA improves adiponectin levels while
297 obesity decreases them [20,28]. In this sense, PA should be promoted for the prevention
298 of cardiovascular diseases, even without the reduction of body weight.

299 Some limitations of the current study should be mentioned. First, we considered
300 a minimum of one day of valid wear time in the present study, which can present bias as

301 one day may not be representative of usual habitual PA. Second, the different models of
302 accelerometers used in each study could represent possible variation between study
303 outcomes. Third, the large number of missing data on metabolic variables must be
304 highlighted, being a potential selection bias for the included sample. The main
305 difference between the included and excluded sample was on chronological age,
306 physical activity level and sedentary time. However, age-adjusted estimates such as
307 BMI and mother educational status (a socioeconomic proxy) were not different between
308 the included and excluded sample. Fourth, the use of a continuous outcome has
309 operational advantages, but it is also relevant to recognize that approaches adopting a
310 categorical diagnosis of metabolic syndrome have its advantages as well. Finally, the
311 lack of control of other potential metabolic risk determinants (e.g. energy intake), and
312 the cross-sectional design preclude evidence of causality from the interpretation of the
313 findings. However, the comprehensive sample with device-based monitoring of PA
314 from four different countries represent the main strength of the study. The
315 understanding of the potential effects of different amounts and intensities of PA on
316 health is only possible through objective/device-based measurements. Moreover, we
317 adjusted the analyses for somatic maturation, which is an important potential
318 confounder because of its association with metabolic risk factors, adiposity and physical
319 activity [8,9].
320
321 **CONCLUSIONS**
322 In conclusion, we found that PA attenuates metabolic risk of adolescents with
323 overweight and obesity. Although VPA seems to explain a great part of this attenuation,
324 MPA also appears important for better metabolic profile. During growth and

development, adolescents with overweight and more physical activity show, in general, similar metabolic risk to their counterparts with normal weight.

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Conflict of interest

The authors declare that they have no conflict of interest.

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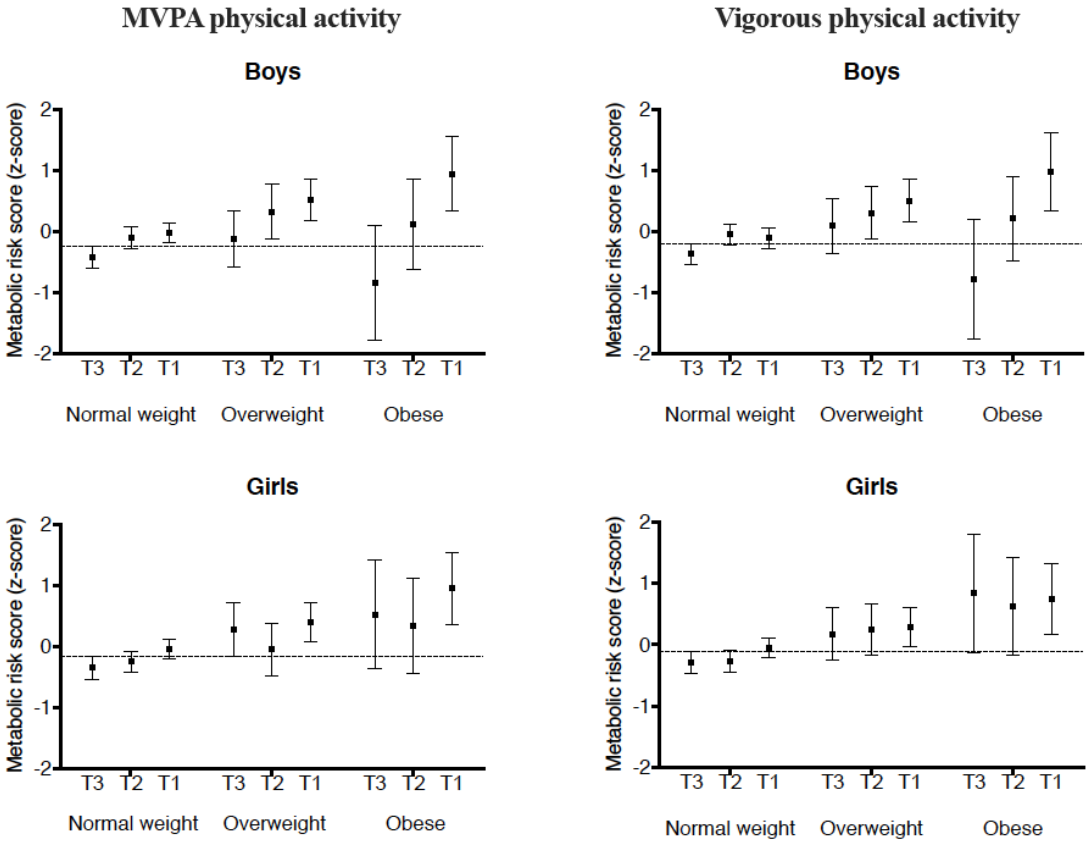

Figure 1. Metabolic risk score according to weight status and tertiles of different intensities of physical activity in adolescents.

Note. Values are presented in estimated marginal means, with 95% confidence intervals. Models were adjusted by accelerometer wear time, study, chronological age, age at peak height velocity, sedentary time and body mass index.

Table 1. Characteristics of the included and excluded sample.

	Included (n=5,216)	**Excluded (n=16,451)**
Chronological age, y	14.6 (14.6 to 14.7)	12.4 (12.4 to 12.5)
Sex (male), %	48.7 (47.0 to 50.3)	47.4 (46.7 to 48.2)
Mothers' education*, %	51.4 (49.7 to 53.0)	53.7 (52.7 to 54.6)
MVPA, min/day	44.7 (43.9 to 45.5)	51.3 (50.9 to 51.7)
VPA, min/day	14.5 (14.1 to 14.9)	15.5 (15.3 to 15.7)
ST, (min/day)	449.2 (446.0 to 452.4)	384.2 (382.7 to 385.7)
APHV, y	12.5 (12.4 to 12.5)	12.2 (12.1 to 12.2)
Body mass index		
Normal weight, %	79.5 (78.4 to 80.6)	80.8 (80.2 to 81.4)
Overweight, %	14.4 (13.5 to 15.4)	14.1 (13.6 to 14.7)
Obese, %	6.1 (5.5 to 6.8)	5.1 (4.8 to 5.4)

Note. Values are presented in mean/frequency and 95% confidence intervals. MVPA, moderate to vigorous physical activity. VPA, vigorous physical activity. ST, sedentary time. APHV, age at peak height velocity. *Threshold: "any post-compulsory education including vocational training", data is available for 3,497 of included participants and 10,726 of not-included participants.

Table 2. Characteristics of the included sample by sex (n=5,216).

	Sex	
	Boys (n=2,486)	**Girls (n=2,730)**
Chronological age, y	14.6 (14.5 to 14.7)	14.7 (14.6 to 14.8)
Age of peak height velocity, y	13.1 (13.1 to 13.2)	11.9 (11.8 to 11.9)
Physical activity, min/d		
Moderate	35.1 (34.3 to 35.9)	25.6 (25.0 to 26.1)
Vigorous	18.9 (18.2 to 19.5)	10.6 (10.2 to 11.0)
Sedentary time, min/d	434.9 (430.2 to 439.7)	462.2 (458.0 to 466.4)
Wear time, min/d	809.6 (805.4 to 813.8)	804.9 (801.3 to 808.5)
Body mass index, kg/m^2	20.9 (20.7 to 21.1)	21.5 (21.3 to 21.6)
Normal weight, %	80.0 (78.3 to 81.5)	79.1 (77.6 to 80.6)
Overweight, %	13.9 (12.6 to 15.3)	14.8 (13.5 to 16.2)
Obese%	6.1 (5.2 to 7.1)	6.1 (5.2 to 7.0)
Waist circumference, cm	73.9 (73.4 to 74.4)	72.6 (72.1 to 73.0)
Systolic blood pressure, mmHg	114.9 (114.4 to 115.4)	110.1 (109.7 to 110.6)
Diastolic blood pressure, mmHg	61.6 (61.3 to 62.0)	62.9 (62.6 to 63.2)
Fasting glucose, mmol/L	5.22 (5.20 to 5.25)	5.05 (5.04 to 5.07)
HDL-C, mmol/L	1.34 (1.32 to 1.35)	1.42 (1.40 to 1.43)
Triglycerides, mmol/L	0.82 (0.80 to 0.84)	0.87 (0.85 to 0.88)
Metabolic risk score, score	-0.07 (-0.16 to 0.01)	-0.07 (-0.15 to 0.02)

Note. Values are presented in means and 95% confidence intervals.

Table 3. Combined association between body mass index, different intensities of physical activity and metabolic risk among adolescents (n=5,216).

	Boys		**Girls**	
	β (95% CI)	r^2	β (95% CI)	r^2
Single model		0.177		0.107
Body mass index	**0.215 (0.194 to 0.236)**		**0.161 (0.142 to 0.181)**	
Vigorous PA		0.180		0.108
Body mass index	**0.213 (0.191 to 0.234)**		**0.161 (0.141 to 0.180)**	
Vigorous PA	**-0.009 (-0.014 to -0.003)**		**-0.008 (-0.016 to -0.001)**	
Moderate to vigorous PA		0.185		0.110
Body mass index	**0.212 (0.191 to 0.233)**		**0.161 (0.141 to 0.180)**	
Moderate to vigorous PA	**-0.008 (-0.011 to -0.005)**		**-0.007 (-0.011 to -0.003)**	

Note. Models were adjusted by accelerometer wear time (when including PA intensities), sedentary time, study, chronological age and age at peak height velocity. CI, confidence interval. PA, physical activity. Values in bold represents $p < 0.05$.

Table 4. Regression models to the role of body mass index and moderate vigorous activity on metabolic risk according tertiles of vigorous physical activity in normal weight and overweight/obese adolescents.

	β	95% CI
Normal weight		
VPA Tertile 1		
Body mass index	**0.166**	**0.114 to 0.217**
Moderate PA	**-0.011**	**-0.021 to -0.001**
VPA Tertile 2		
Body mass index	**0.090**	**0.034 to 0.147**
Moderate PA	-0.008	-0.017 to 0.000
VPA Tertile 3		
Body mass index	**0.108**	**0.052 to 0.165**
Moderate PA	**-0.013**	**-0.020 to -0.006**
Overweight/obese		
VPA Tertile 1		
Body mass index	**0.166**	**0.118 to 0.214**
Moderate PA	-0.001	-0.023 to 0.021
VPA Tertile 2		
Body mass index	**0.175**	**0.101 to 0.249**
Moderate PA	**-0.027**	**-0.052 to -0.003**
VPA Tertile 3		
Body mass index	**0.205**	**0.104 to 0.306**
Moderate PA	-0.012	-0.035 to 0.011

Note. Models were adjusted by sex, accelerometer wear time, sedentary time, study, chronological age and age at peak height velocity. CI, confidence interval. PA, physical activity. Values in bold represents $p < 0.05$.