Associations of Vigorous-intensity Physical Activity with Biomarkers in Youth

Short title: Vigorous Physical Activity, Biomarkers, Youth

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Abbreviations: CPM – Counts per minute; HDL – High Density Lipoprotein; ICAD – International Children's Accelerometry Database; LDL – Low Density Lipoprotein; MPA – Moderate Physical Activity; MVPA – Moderate-to-vigorous Physical Activity; VPA – Vigorous Physical Activity; WC – Waist Circumference.

ABSTRACT

Introduction: Physical activity (PA) conveys known cardiometabolic benefits to youth, but the contribution of vigorous-intensity PA (VPA) to these benefits is unknown. Therefore, we sought to determine, a) the associations between VPA and cardiometabolic biomarkers independent of moderate-intensity PA (MPA) and time sedentary, and b) the accelerometer cutpoint that best represents the threshold for health-promoting VPA in youth.

Methods: Data from the International Children's Accelerometry Database (ICAD) were analyzed in 2015. The relationship between cardiometabolic biomarkers and 4 categories of VPA estimated via 3 sets of cutpoints were examined using isotemporal substitution quantile regression modeling at the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentile of the distribution of each biomarker, separately. Age, sex, accelerometer wear time, sedentary time, and MPA were controlled for while allowing substitution for light-intensity PA. Data from 11,588 youth (4-18yrs) from 11 ICAD studies (collected 1998-2009) were analyzed.

Results: Only 32 of 360 significant associations were observed. Significant, negative relationships were observed for VPA with waist circumference and insulin. Replacing light intensity PA with VPA (corresponding to at the 25^{th} to 90^{th} percentiles of VPA) was associated with a .67 (-1.33, -0.01; P = .048) to 7.30cm (-11.01, -3.58; P < .001) lower waist circumference using Evenson and ICAD cutpoints (i.e., higher CPM). VPA levels were associated with 12.60 (-21.28, -3.92; P = .004) to 27.03 pmol/l (-45.03, -9.03; P = .003) lower insulin levels at the 75^{th} to 90^{th} percentiles using Evenson and ICAD cutpoints when substituted for light PA.

Conclusions: Substituting light PA with VPA was inversely associated with waist circumference and insulin. However, VPA was inconsistently related to the remaining biomarkers after controlling for time sedentary and MPA.

Keywords: Movement; cardiometabolic; adiposity; insulin.

INTRODUCTION

Emerging research utilizing international samples (7, 17) has indicated that many children globally are spending an insufficient amount of time engaging in physical activity (PA) and an excessive amount of time engaging in sedentary behaviors. Engaging in international guideline recommendations (38) of 60 minutes per day (min/day) of moderate-to-vigorous physical activity (MVPA) is inversely associated with biomarkers of cardiometabolic health (13, 25) including lower rates of obesity (17) independent of time spent sedentary. While the benefits of MVPA are well established cross-sectionally (7) and longitudinally (6), few studies of PA in youth have examined the contribution of specific intensities to the association, despite a growing body of literature that suggests that vigorous-intensity physical activity (VPA) may be more important for the prevention and amelioration of cardiometabolic risk factors (13, 39). A small number of studies have employed an objective measure of PA to examine associations with cardiometabolic biomarkers. These studies suggest that VPA is independently associated with cardiorespiratory fitness (positive) (23), BMI (negative) (17), adiposity (negative) (32), HDL cholesterol (positive) (22), fasting glucose (negative) (31), and fasting insulin (negative) (1). However, an extensive examination of the literature suggests that the relationship between VPA and cardiometabolic biomarkers is inconsistent, potentially due to small samples, definition of VPA, and other methodological limitations (11).

Complicating examinations of the relations between VPA and cardiometabolic biomarkers is an issue of measurement of VPA, or more specifically, the threshold for which VPA occurs. While imperfect, accelerometers are still considered one of the best objective measures available for epidemiological studies of PA (5, 28), but the processing of data generated by accelerometers

(e.g., "counts") lacks uniformity or consistency across studies (18), which can lead to misclassification of exercise intensity (12) and/or lack of comparability across studies (3, 4). Since the choice of cutpoint is a de facto selection of an intensity threshold with all other sources of variability held constant (e.g., monitor brand, epoch), and no standard exists for the VPA cutpoint, it is imperative to consider a range of accelerometer cutpoints for VPA if the relationship between VPA and cardiometabolic biomarkers is to be studied.

The benefits of MVPA in youth are well established, but little research has been conducted to examine the contribution of PA intensity in cardiometabolic health in youth. Therefore, the objective of the present investigation was to determine, a) the associations between VPA and cardiometabolic biomarkers independent of moderate physical activity (MPA) and sedentary time, and b) the accelerometer cutpoint that best represents the threshold for health-promoting VPA in a diverse sample of youth.

MATERIALS/SUBJECTS AND METHODS

Study Design

Data were utilized from the International Children's Accelerometry Database (ICAD, http://www.mrc-epid.cam.ac.uk/Research/Studies/), which was established to pool data on PA from studies in youth worldwide. A comprehensive description of the ICAD can be found elsewhere (34). Briefly, in 2008 19 studies were identified from a PubMed search that used an Actigraph (Actigraph, LLC, Pensacola, FL, USA) accelerometer and included a minimum of 400 participants aged 3 to 18 years. Six additional studies were identified through professional colleagues, with 21 studies ultimately contributing data to the final database (7, 34). For the

current study, 11 studies were included (7, 34), which are presented in brief with the variables each contributed in Table 1 [details of the Avon Longitudinal Study of Parents and Children (ALSPAC) are available at www.bris.ac.uk/alspac and including the data that are available via a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary)]. Ethical approval for the present study was attained from participating institutions, and data-sharing agreements were established prior to contribution of data.

Participants

Data from 11,588 youth (4-18yrs), representing 11 studies from Brazil, Europe, and the United States from the ICAD were analyzed. Data from studies conducted between 1998 and 2009 were included in the present analyses if the dataset contained PA, age, sex, and at least one biomarker of a cardiometabolic risk [defined as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (2)].

Measurements

Physical activity. A comprehensive description of the measurement of PA has been published previously (34). ICAD data were reanalyzed to allow for comparability across studies by aggregating data to a 60-second epoch. The criterion of 60 minutes of consecutive zeros was utilized to designate non-wear time, with a tolerance for 2 minutes of nonzero epochs (35). Participants with three or more days with 600 minutes of valid wear time were included in analyses. VPA was defined by cutpoints from Pate (26), Evenson (8), and the ICAD workgroup (7, 34). These cutpoints were selected because they represent the most generous, lowest

threshold defining VPA [Pate ≥ 3,365 counts/min (CPM)], a medium threshold (Evenson ≥ 4,012 CPM), to the most stringent, highest threshold for VPA (ICAD ≥ 6,000 CPM).

Cardiometabolic biomarkers. Eight cardiometabolic biomarkers reflecting a diverse array of health indices were collected, including; waist circumference [as a proxy for adiposity (30)]; systolic and diastolic blood pressure (hemodynamics); high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting triglycerides (lipid metabolism); fasting glucose and fasting insulin (glucose metabolism). Details of data collection procedures can be found elsewhere (7, 34). Waist circumference (WC) was assessed midway between the lower rib margin and the iliac crest using a metal tape (10), except in the NHANES (National Health and Nutrition Examination Survey) where WC was measured just above the iliac crest at the mid-axillary line using similar equipment (36). Resting blood pressure was measured using standard procedures, reported previously (7). Markers of lipid and glucose metabolism were assessed using standard clinical procedures described in detail elsewhere (36).

Statistical Analysis

Descriptive analyses of accelerometer-derived estimates of min•day^{-1} spent in sedentary, MPA, and VPA were computed across all studies using three sets of cutpoints to define PA intensities. To evaluate the cross-sectional association of cardiometabolic biomarkers and time spent in VPA, a series of isotemporal substitution quantile regression models were estimated for each set of cutpoints separately (20, 21, 40). Quantile regression models were employed since biomarkers are often non-normal in their distribution, and quantile regression models are not influenced by normality and are free from distributional assumptions (19). Individual models for each

93 biomarker as the dependent variable were estimated. Time spent in VPA, defined by one of the 3
94 sets of cutpoints, separately, served as the primary independent variable. Because of its non-
95 normal distribution, min•day^{-1} spent in VPA was placed into 4 categories – none (0mins/d –
96 reference category), low (lower 33%), middle (middle 33%), and high (upper 33%) – based on
97 the distribution of VPA for each of the 3 sets of cutpoints. The relationship between cardio-
98 metabolic biomarkers and 4 categories of VPA min/d [none (0 min/d – reference category), low
99 (7.2_{Pate}, $4.0_{Evenson}$, 1.5_{ICAD} min/d), medium (18.6_{Pate}, $11.0_{Evenson}$, 3.5_{ICAD} min/d), and high (42.7_{Pate},
100 $28.9_{Evenson}$, 11.9_{ICAD} min/d)] estimated via 3 sets of cutpoints [Pate: sedentary = 0 - 152
101 counts/min (CPM), MPA = 1677 – 3364, VPA = ≥ 3,365 CPM; Evenson: sedentary = 0 - 100
102 CPM, MPA = 2296 – 4011, VPA = ≥ 4,012 CPM; and ICAD: sedentary = 0 - 100 CPM, MPA =
103 3000 – 6000, VPA = ≥ 6,001 CPM] —were examined using isotemporal substitution quantile
104 regression modeled at the 10th, 25th, 50th, 75th, and 90th percentiles of the distribution of each
105 biomarker. Included in each model were age (years), sex, average total daily wear time, and
106 min•day^{-1} in sedentary and MPA distilled using the corresponding cutpoint for VPA. Since light
107 PA (LPA) was the only intensity excluded from the models, all estimates are interpreted as
108 substituting "x" amount of LPA with VPA. Separate models were estimated for each study and
109 for each set of cutpoints used to define VPA within each study. An example of the modeling
110 approach is: insulin serving as the dependent variable, with 3 separate models using VPA levels
111 (i.e., low, middle and high, with no VPA as the referent group) reduced with each of the sets of
112 cutpoints for each study, run separately. Statistical significance was set at P = .05.
113
114 Meta-analytical techniques were used to combine the quantile regression model coefficients and
115 standard errors for each biomarker across the 11 studies for each of the 3 sets of cutpoints,

116 separately. Random effects inverse variance weighting was used to pool effects across studies
117 and within study for each set of cutpoints. The study served as the unit of analysis for each
118 quantile and category of VPA. For instance, the VPA estimates representing the lowest 33rd of
119 the distribution of VPA regressed on the 10th quantile of insulin were combined across all studies
120 for a given biomarker. All quantile regression analyses were conducted in 2015 using Stata
121 (v.13.0, College Station, TX) and all meta-analytic analyses were conducted using
122 Comprehensive Meta-Analysis (v2.2, Englewood, NJ).
123
124 **RESULTS**
125 Descriptive information for each study is presented in Table 2. The average amount of VPA
126 min•day^{-1} for each set of cutpoints (highest to lowest) by tertile ranged from 1.5 to 7.2 min/day
127 for the lowest tertile, the medium tertile 3.5 to 18.6 min/day, and the highest tertile 11.9 to 42.7
128 min/day. The results of the pooled meta-analytic effects for each quantile and level of VPA
129 across each cardiometabolic biomarker are presented in Table 3.
130
131 **Relationship of volume of VPA with cardiometabolic biomarkers**
132 Substituting LPA with VPA was inconsistently related to systolic/diastolic blood pressure,
133 fasting triglycerides, HDL, or LDL after controlling for time sedentary and MPA at all tertiles of
134 VPA volume, with only 32 of a possible 360 associations statistically significant ($P < .05$).
135 Independent of min•day^{-1} spent sedentary and in MPA, substituting LPA with VPA was
136 associated with a .67 to 7.30 cm smaller waist circumference at the 50th to 90th percentiles.
137 Relationships were observed for all three tertiles of VPA, but relationships at the lowest tertile of
138 VPA volume were significant at only the highest cutpoint value (i.e., ICAD). Substituting LPA

with VPA was associated with 12.6 to 27.0 pmol/l lower insulin values at the 75th to 90th percentiles. Relationships were observed for all three tertiles of VPA, but relationships at the lowest tertile of VPA were significant at only the highest tertiles of VPA volume for the highest cutpoint value (i.e., ICAD).

Influence of cutpoint

Independent of min•day^{-1} spent sedentary and in MPA, substituting LPA with the high volume of VPA defined via Pate cutpoints was associated with a smaller waist circumference only at the 90th percentile. For VPA determined via Evenson cutpoints, substituting LPA for medium and high VPA levels were associated with a smaller waist circumference at the 25th to 90th centiles. Substituting LPA with the lowest, medium, and highest volumes of VPA reduced via ICAD cutpoints was associated with a smaller waist circumference at the 50th to 90th, the 75th and 90th, and the 25th to 90th, respectively. Across all other biomarkers (i.e., SBP, DBP, HDL, LDL, glucose, and triglycerides), no consistent associations or patterns were observed, with only 9 significant associations observed from a possible 270 tested (<5%; see Figure).

DISCUSSION

The present study is the first of this scope (e.g., sample size, diversity of national origin) to examine the relationship between VPA and cardiometabolic biomarkers in youth. The results are consistent with previous studies using more homogeneous samples, such as Carson et al. (6) where no association was found between diastolic blood pressure and VPA, but a significant negative association was reported between waist circumference and VPA in children of the 2nd and 3rd quartiles (relative to the 1st). The more nuanced analyses presented here, taken with those

of Carson et al. (6), provide additional insight into the complex relationship between VPA and cardiometabolic biomarkers (11, 25). The results suggest that substituting modest amounts of LPA for VPA may have cardiometabolic benefits above and beyond those conveyed by MPA and avoidance of sedentary behavior (24). Of potentially greater importance, the current results suggest that these health supportive associations are most pronounced in those who have undesirable levels of these biomarkers, specifically those with relatively large waist circumference or fasting insulin levels. If these relationships are found to be robust in longitudinal and experimental studies, then a specific frequency and duration of VPA could be incorporated as a distinct component of a PA "prescription" for youth (24). However, it must be noted that VPA was independently associated with only two of the markers examined. Therefore, while VPA may relay meaningful health benefits, the number of markers exhibiting those benefits may be few relative to less intense movement.

These results, taken with a growing body of literature demonstrating the independent health benefits of VPA for youth (6, 11, 14, 16, 17, 23, 24, 37), support the assertion that this intensity should be considered when setting policy recommendations for PA of youth. For example, it has been shown previously that as little as 9 (15) to 14 minutes (17) of VPA per day is associated with less adiposity in Canadian (15) and multinational samples of youth (17). These previous findings, derived from independent samples, are consistent with the present findings showing an association of substituting 11.9 to 42.7 min/day of LPA for VPA. While this is a considerable range, with the top end (42.7 min/day) potentially impractical, consistent benefits were seen for VPA defined by the ICAD cutpoints, which even in the high volume category represented 11.9 min/day of VPA, is potentially achievable for most youth (39). Therefore, the present findings

185 suggest a modest duration (e.g., approximately 10 min) of high intensity PA may be related to
186 health benefits in youth who exhibit undesirable levels of insulin or waist circumference.
187
188 While the present study has a number of strengths, including an objective measure of PA, a large
189 sample size, a diverse and international sample, and an advanced analytical approach, the present
190 results should be considered in light of a number of limitations. First, all data were cross-
191 sectional in nature, therefore causality cannot be assumed. For example, it is possible that
192 children with smaller waist circumference are more vigorously active because it is less
193 cumbersome for them to do so. However, the nature of our analyses, which examined the
194 relationship of VPA and waist circumference at different quantiles of waist circumference, is less
195 supportive of this possibility. Second, while these cross-sectional results are supportive of VPA
196 specific PA recommendations for youth, it is unknown if changes in youth VPA levels will result
197 in meaningful changes in diastolic blood pressure, HDL, cholesterol, insulin or adiposity. While
198 a recent study is supportive of the latter three (29), the literature is mixed on the relationship
199 between increased VPA and blood pressure (9, 11, 27, 33), and very few studies have examined
200 the responsiveness of insulin or other markers of glucose metabolism (11, 13). Third, the
201 database we utilized lacks standardized dietary data or genetic data that might confound the
202 observed relationships. For example, children with higher levels of VPA may consume fewer
203 calories, or possess a genetic make-up supportive of a positive biomarker profile. This possibility
204 cannot be ruled out using the currently available data. Despite these limitations, this study
205 represents one of the largest to date that examined VPA in relation to cardiometabolic
206 biomarkers in youth.
207

In summary, the present results suggest few significant or clinically meaningful associations between VPA and most cardiometabolic biomarkers studied in youth, but health promoting associations were observed between VPA and select cardiometabolic biomarkers (i.e., insulin, waist circumference), with the associations observed at higher levels of the biomarkers and higher volumes of VPA. As such, VPA may have unique metabolic health benefits beyond those conveyed by MPA or minimizing time spent sedentary. The present results also suggest that higher VPA cutpoints represent an intensity that is associated with healthier insulin levels and waist circumference. Future longitudinal and intervention studies are needed to determine the temporal relationship between these variables, the modifiability of VPA, and the effect of increased VPA on biomarkers in youth. If these results are indeed robust, then a less time consuming, more intense dose of PA may be a viable option for youth seeking to achieve or maintain cardiovascular health.

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