Objectively-measured physical activity and its association with adiponectin and other novel metabolic markers: a longitudinal study in children (EarlyBird 38)

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Objective: Recent evidence suggests that, in children, traditional markers of metabolic disturbance are related only weakly to physical activity (PA). We therefore sought to establish the corresponding relationships with newer metabolic markers.

Research Design and Methods: This is a non-intervention longitudinal study of 213 healthy children recruited from 54 schools in Plymouth, UK. MTI accelerometers were used to make objective seven-day recordings of PA at ages 5y (SD ±0.3y), 6y, 7y and 8y. Overall PA was taken as the average of the four annual time points. The metabolic markers at 8y were adiponectin, leptin, high sensitivity C-reactive protein (hsCRP) and insulin resistance (HOMA-IR). Potential confounders included percent body fat (%BF) measured by DEXA and diet measured by food frequency questionnaire.

Results: While PA did not correlate with IR (r=-0.01), leptin (r=+0.04) or hsCRP (r=+0.01) independently of %BF, it did with adiponectin, but inversely (r=-0.18 p=0.02). This unexpected inverse relationship was strongest among the less active children (PA<median: r= -0.30, p=0.01) but negligible in the more active children (PA>median: r=+0.04, p=0.76). Adiponectin was significantly higher (0.52SD, p<0.01) in the least active tertile compared to the other two tertiles. Insulin resistance, however, did not differ across the PA tertiles (p=0.62).

Conclusions: Adiponectin levels in children are highest among those who are least active but their insulin resistance is no different. Adiponectin has a known insulin-sensitizing effect, and our findings are consistent with a selective effect at low levels of physical activity.
Childhood obesity is increasing throughout the industrialized world, and both inactivity and over-nutrition are believed to contribute (1). Obesity is of concern because it drives the insulin resistance that is believed to underlie diabetes, cardiovascular disease and metabolic syndrome (2).

Two reviews looking at the relationship between PA and the traditional metabolic markers in children report only weak associations. Wareham and colleagues reviewed 12 such studies relating habitual PA to insulin resistance and found five that reported a weak-to-moderate correlation (3). Froberg and Andersen reported similar findings with studies measuring physical activity and lipids, where five reported no association and the remaining six a weak association (4). The same review also reported six studies which investigated the relationship between PA and blood pressure, where three found an association and three did not.

Markers such as leptin, adiponectin and CRP have received less attention with respect to PA, although all three show weak-to-moderate associations with the traditional markers of metabolic health in children. Leptin appears to be positively correlated with insulin resistance (5), and adiponectin inversely correlated (6), though Ong et al. did suggest a weak positive association for adiponectin in boys (7). A study of adolescents reported significantly higher CRP levels in young males with three or more traditional risk factors compared to males who had fewer, though no such association was found in young females (8).

Thus, while there are (weak) associations in children between PA and the more traditional metabolic markers, the newer markers do not appear simply to be surrogates for them. Given that the mechanisms whereby PA improves metabolic health are incompletely understood, and that metabolic disease is believed to be an inflammatory state (9), it seemed appropriate to consider whether the impact of PA on metabolic health might be mediated by, or reflected in, adipokines (e.g. adiponectin and leptin) and/or inflammatory reactants (e.g. hsCRP).

Only five studies of children/adolescents have investigated the relationship between PA and one or more of these novel metabolic markers (10-14). Three studies out of three reported no significant association between PA and adiponectin (10,12,13), and only one out of three reported an association with CRP (14). Two of two reported that serum leptin was inversely related to PA, independently of body composition (10,11). However, none of these five studies measured PA objectively. Three were exercise training intervention studies (11,13,14) and the other two were cross-sectional studies that measured physical activity using self-report questionnaires (10,12).

In this study we have investigated the relationships between PA and three of the more recent markers of metabolic disturbance using an objective measure of PA whose reliability was optimized by a longitudinal design.

**RESEARCH DESIGN AND METHODS**

**Design and participants:** EarlyBird is a non-intervention prospective cohort study of 307 healthy children (170 boys, 137 girls). The children were recruited at age 4.9±0.3y (school entry: January 2000 to January...
Physical activity and novel metabolic markers

2001) from 54 Plymouth schools. Schools were stratified into quartiles according to proportion of pupils entitled to free school meals. A random selection was made from each, ensuring a wide socio-economic mix representative of the Plymouth area (Index of multiple deprivation 2004 score: cohort=26.1, Plymouth=26.3, England=21.7). Most (98%, n=302) were white Caucasian and five children (2%) were of mixed race, reflecting the racial mix of the area. Local Research Ethics Committee approval was obtained in 1999, and the study's rationale, recruitment procedures and protocol have been reported in detail elsewhere (15).

Measurements: Physical activity—MTI Actigraphs (formerly CSA accelerometers, Fort Walton Beach, Florida, US) are small (50 x 41 x 15mm), lightweight (43g), robust, tamperproof, of good technical reproducibility (between-monitor CV=5% and within-monitor CV<2%, (16)) and correlate well with criterion measures of free-living activity-related energy expenditure by indirect calorimetry (r=0.92 with body weight (17)). They record change in vertical acceleration 600 times per minute which for the present study data was integrated into one-minute epochs. The Actigraphs were worn on an adjustable, elastic belt around the child’s waist and were set to run continuously for seven days at each of the four annual time-points – 5y, 6y, 7y and 8y (mean interval between follow-ups =1.0y, SD=1mth). The children were asked to wear the Actigraph everyday from when they got up in the morning to when they went to bed at night, only taking it off for water-based activities (e.g. swimming, bathing, showering etc.). The Actigraphs were worn during the week that followed the measurement of metabolic health in order to eliminate any acute effect that PA may have on such factors. Parental-reported periods of non-compliance and periods with zero accelerometer counts for ≥17 consecutive minutes (assumed to be unreported non-compliance) were replaced with the mean of counts recorded at the same clock time on the other days. The sensitivity of each accelerometer was measured, under controlled conditions, by a motorized turntable (16). Seasonality was measured on a continuous scale by the number of relevant daylight hours (from 8am to 9pm) for the week the accelerometer was worn.

Two components of physical activity were calculated from the Actigraph data: total PA volume and minutes spent in moderate-and-vigorous intensity activities (MVPA). MVPA here is equivalent to ≥3 METs (18) (resting energy expenditure = 1 MET) and equates to ≥2500 Actigraph counts/min. Others have equated 3 METs to a walking speed of ~4km/h (18) and our own calibration trials (unpublished) indicate that pre-pubertal children walking at 4km/h average ~2500 Actigraph counts/min. These are similar to calibration data reported by Schmitz et al. (8-12y olds walking at 4km/h = 3.2 METs = 2359 counts/min (17)). We have reported previously that the average of two annual time-points of physical activity recordings is required to provide >80% reliability in ranking/positioning individual children (19). For this reason, only children who wore the Actigraph on at least two of the four annual time-points (each for a minimum of 9 hours/day for ≥5 days) were deemed to have a sufficiently reliable measure of PA.

Diet: A validated food frequency questionnaire, completed by the parents, was used to measure the quality of the child’s diet (20) at each of the four annual
time-points. The frequency of foods consumed per week that were either high in fat or high in sugar were derived from eleven and six questions respectively.

**Body fat:** %BF at age 8y was obtained from a whole body dual-energy x-ray absorptiometry (DEXA) scan performed with the Lunar DPX-L pencil beam Densitometer. Body mass index (BMI) was calculated from measures of weight and height and age-adjusted standard deviation scores (SDS) for BMI were derived from 1990 UK reference data.

**Metabolic markers:** A venous blood sample was taken at ~9am after an overnight fast. Serum insulin was measured using an Immulite analyser (Diagnostic Products Corporation, USA). The cross-reactivity with proinsulin was <1%, the inter-assay coefficient of variation (CV) was ~9% and the detection limit of the assay was 2.0 mU/l. Glucose was measured using a Cobas Integra 700 analyser (Roche Diagnostics, UK), with inter-assay CV being ~2%. The values for insulin and glucose were used to derive a measure of insulin resistance using the HOMA-IR program. HOMA-IR has been validated against the euglycemic clamp (r=0.91) in healthy children (21). Adiponectin, leptin, and high sensitivity C-reactive protein (hsCRP) were measured on thawed serum (stored at -85°C for between 6-18 months) at the Department of Vascular Biochemistry, University of Glasgow. Adiponectin was measured by ELISA (R & D Systems, UK) with inter-assay CV being 7%. Leptin was measured by an ‘in house’ radioimmunoassay validated against the commercially available Linco assay. The inter-assay CV was <10% over the sample concentration range and the detection limit of the assay was 0.5ng/ml. CRP was measured by automated particle-enhanced immunoturbidimetric assay (Roche Diagnostics, UK). The method has a lower limit of sensitivity of 0.1mg/l and inter-assay CV of <3%.

**Statistical analysis:** Each seven-day sample of physical activity was adjusted for seasonality and for the sensitivity of each Actigraph device prior to averaging the annual recordings. Diet quality was also averaged over the four annual time-points. The distribution of BMI, %BF and all four metabolic markers were positively skewed and therefore all analyses were carried out on log transformed data. Analysis of covariance was performed, controlling for age, to establish gender differences for physical activity, BMI, %BF and the four metabolic markers. Means (95% CI) of logged data were back-transformed. Hierarchical linear regression analysis was performed to quantify the association between physical activity (total PA and MVPA) and the metabolic markers with i) age and ii) age, diet and %BF already entered into the model as potential confounders. This regression analysis was carried out on boys and girls separately and together (controlling for gender). Analysis of covariance also compared the distribution of insulin resistance and adiponectin (both internally derived SD-scores) across tertiles of physical activity independent of gender, age, diet and %BF.

All data analysis was carried out using SpSS ver.14.0.

**RESULTS**

**Attrition/compliance:** During the three-year period (5-8y), 21 boys and 16 girls of the 307 recruited left the study. There was no difference in the baseline BMI-SDS between those who left by the 8y visit and those who remained (difference = 0.06SDS, p=0.76). Of the
270 children who remained in the study at 8y, one child was entering puberty (established by a detectable level of the luteinising hormone), 30 children did not have a sufficiently reliable measure of PA and a further 18 children did not have a measure of body fat from DEXA. Of the remaining 221 children a further 8 to 19 children did not have a measure for one or more of the metabolic markers. The final analyses were therefore based on 202 to 213 children (55% boys) depending on the risk factor being analysed. There was no difference in BMI-SDS at 8y between those included and those excluded from the analysis (difference = 0.03SDS, p=0.85) Sample sizes of n≥200 can deem partial correlations of r≥0.20 statistically significant (p<0.05) with 80% power.

Subject characteristics: A summary of the subject characteristics by gender is presented in Table 1. The girls were less active than the boys spending, on average, 11 mins/day less in MVPA. The frequency with which children consumed foods that were high in fat or high in sugar foods did not differ by gender. The BMI (kg/m² and age/gender-specific SDS) and %BF was significantly higher in the girls than in boys. Levels of HOMA-IR, leptin and hsCRP were significantly less favorable (higher) in the girls yet their levels of adiponectin were slightly, though not significantly, more favorable (higher) than boys.

Associations: Table 2 reports the associations between physical activity (total PA and MVPA) and the metabolic markers. There were no clinically or statistically significant associations in either sex between physical activity and insulin resistance, leptin or hsCRP, before or after controlling for diet and %BF. In girls, there were moderate inverse correlations between physical activity and adiponectin which strengthened slightly after adjustment for diet and %BF. The association was strongest for MVPA, explaining nearly 11% (r= -0.33, p<0.01) of the variation in adiponectin. The corresponding associations in the boys were also inverse though weaker and not statistically significant (r= -0.13, p=0.21). When combining all children (controlling for gender) the overall association between physical activity and adiponectin was significant (r=-0.20, p=0.01). Further analysis revealed that this inverse linear relationship was largely attributable to the children whose PA lay below the median (r= -0.31, p<0.01) rather than those above the median (r= +0.05, p=0.68) where the gradient of association leveled off (interaction term: p=0.03). A model containing a logarithmic function of PA confirmed this curvilinear association over the entire range of PA, improving the r-value slightly from -0.20 to -0.23.

Figure 1 shows mean insulin resistance and adiponectin (both internally derived SD-scores) by tertile of physical activity. While levels of insulin resistance did not differ across the tertiles (p=0.47), adiponectin was significantly higher (effect size: 0.52SD, p<0.01) in the least active group compared to the middle and most active groups who had similar adiponectin levels to each other (effect size: 0.02SD, p=0.96).

CONCLUSIONS
This study in children reports findings similar to those of others for insulin resistance, leptin and hsCRP, but reveals an association with adiponectin that has not previously been reported. Insulin resistance, leptin and hsCRP measured at age 8y were unrelated to PA. Adiponectin, on the other hand, was inversely related to PA and remained so
after adjustment for body fat and diet quality. This finding seems at first sight paradoxical, given that lower metabolic risk in children is reportedly associated with both higher PA (3,4) and higher adiponectin (6).

Of the three previous studies to have investigated the link between PA and adiponectin in children (10,12,13), two showed trends consistent in direction with the findings of the present study, but neither reached statistical significance. Platat et al. reported that adiponectin levels were 9% higher (effect size ~ 0.2SD, p=0.09) in the least physically active tertile compared to the most active tertile (10). Nassis et al. found that the mean adiponectin level was 5% higher (effect size ~ 0.2SD, p>0.05) before, compared to after, a 12-week exercise training programme (13). The smaller effect sizes in these studies compared to those we observed (~ 0.5SD) may be due to methodological differences. Platat et al. used questionnaires to categorise the children according to participation in ‘organised leisure-time physical activity’, rather than total physical activity which may under-estimate differences between the most and least physically active groups. The exercise training programme delivered by Nassis et al. may not have increased ‘total’ PA by as much as intended. This could be due to poor-compliance and/or the possibility that children offset session-related increases with less activity than usual during the rest of the week. Also, Nassis and colleagues measured adiponectin before and after 12 weeks of ‘increased’ activity whereas the present study compares the adiponectin levels between groups of children whose average activity levels have been very different for at least three years (5-8y).

Yatagia and colleagues studied the relationship between adiponectin and PA in adults and, in line with the findings of Nassis et al. in children, found that serum adiponectin fell significantly in response to a six-week exercise training programme in men (n=12) (22). Despite a strong inverse relationship between insulin resistance and adiponectin prior to the intervention (r= -0.63), the pre- to post-intervention decrease in adiponectin was accompanied by a decrease in insulin resistance (measured by intravenous glucose tolerance tests), though fasting insulin did not change. The authors suggested that ‘increased insulin action induced by the exercise’ may suppress the expression and/or secretion of adiponectin. This interpretation is supported by the in vitro study by Fasshauer et al. that demonstrated a dose-dependent reduction in the expression of adiponectin mRNA in 3T3-L1 adipocytes in response to insulin (23). Our data is consistent with this insofar as adiponectin levels were higher in the least active tertile of children, while insulin resistance remained constant across the PA range. We interpret the observation to mean that when levels of PA are insufficient to maintain insulin sensitivity, adiponectin may be secreted to compensate. In support of this hypothesis, we found that the association between adiponectin and insulin resistance differed by activity group. Although the interaction fell just short of statistical significance (p=0.08) the correlation between adiponectin and insulin resistance appeared to be stronger when PA levels were lower (PA<median r= -0.21 vs PA>median r= +0.08). A review of the adult literature was also consistent with this hypothesis where 11 out of 14 studies showed that exercise decreased insulin resistance (or
surrogate of it) without changing adiponectin (24). These findings suggest that the compensatory secretion of adiponectin may not be required when PA levels are sufficient to improve insulin sensitivity.

The weak independent association between PA and insulin resistance shown in the present study \((r= -0.07 \text{ to } 0.00)\) is consistent with the reports reviewed by Wareham and colleagues (3). Although half of the studies did report a significant inverse association, none of these measured PA objectively. Since that review, the European Youth Heart Study has reported an inverse association \((r= -0.17)\) between objectively-measured PA and insulin resistance in older children \((9y \text{ to } 15y)\), though not independently of body fat (25). Others have found an inverse relationship between leptin and PA \((10,11)\) where the present study did not. CRP was not associated with PA in this study or in two out of the three other studies that have reported it \((10,13)\), suggesting that this marker of low-grade inflammation is not influenced by the level of habitual PA in children. The independent associations of PA with insulin resistance, leptin and hsCRP were never greater than \(r=0.02\) and therefore it would seem unlikely that this study has failed to detect any meaningful, underlying relationships.

This study has strengths and limitations. As the ‘true’ underlying associations between PA and metabolic markers are likely to be subtle, both the exposure and outcome variables need to be measured reliably in order to reveal them. Fewer studies are now using questionnaires to measure PA, and more are using objective assessment methods such as accelerometers which offer a greater degree of reliability. However, although PA is relatively consistent from year-to-year \((r \sim 0.5)\), reliability is lost by sampling just one week of it. By taking the average across two, three or four annual time-points \((\text{mean } 3.5 \text{ in this report})\) we were able to improve the reliability of the PA measure from 71% \((\text{one time-point})\) to 88%. The present study measured ‘total’ adiponectin rather than the ‘high molecular weight’ adiponectin (deemed the biologically active form). However, owing to the less precise measure of biologically active adiponectin, it is unlikely that the associations reported here over-estimate the true underlying association between adiponectin and physical activity. Potential confounders such as age, diet quality and body fat did not account, even partly, for the inverse relationship observed between PA and adiponectin, but in fact appeared to strengthen it. Finally, this study is based on a single population of Caucasian children living in the South West of England. The homogeneity of age and race may have been important to revealing the associations we have reported, but the findings may not be generalisable to other racial groups or to older age groups (adolescents, adults).

To our knowledge, this is the first study to investigate the relationship of adiponectin, leptin and hsCRP to objectively-measured free-living physical activity in children. It may also be the first of its kind to examine the interaction between insulin resistance, adiponectin and physical activity in pre-pubertal children. Although a novel inference, it seems possible that adiponectin is secreted to modulate insulin sensitivity when activity levels are insufficient to do so. Such a compensatory mechanism, if present, would support the concept that adiponectin is a selectively controlled modulator of insulin sensitivity. A
randomised controlled trial would be needed to establish the cause and effect of this relationship.

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Table 1 – Subject characteristics - Mean (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>117</td>
<td>96</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>7.83 (7.76 to 7.90)</td>
<td>7.83 (7.77 to 7.89)</td>
<td>0.92</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total volume (unitsx10^5)</td>
<td>38.1 (36.5 to 39.7)</td>
<td>34.9 (33.7 to 36.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate-and-Vigorous (mins/day)</td>
<td>56.0 (52.0 to 60.0)</td>
<td>45.1 (42.0 to 48.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foods high in fat (frequency/week)</td>
<td>19.0 (18.1 to 19.9)</td>
<td>18.8 (17.8 to 19.8)</td>
<td>0.81</td>
</tr>
<tr>
<td>Foods high in sugar (frequency/week)</td>
<td>21.2 (20.2 to 22.2)</td>
<td>22.0 (20.7 to 23.2)</td>
<td>0.38</td>
</tr>
<tr>
<td>Body composition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI* (kg/m^2)</td>
<td>16.5 (15.8 to 17.2)</td>
<td>17.5 (17.0 to 18.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>0.27 (0.02 to 0.51)</td>
<td>0.56 (0.33 to 0.78)</td>
<td>0.06</td>
</tr>
<tr>
<td>Body fat* (%)</td>
<td>16.4 (14.1 to 18.7)</td>
<td>23.8 (22.0 to 25.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin resistance* (HOMA-IR)</td>
<td>0.37 (0.32 to 0.43)</td>
<td>0.46 (0.41 to 0.51)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adiponectin* a (ug/ml)</td>
<td>11.6 (10.5 to 12.8)</td>
<td>12.6 (11.6 to 13.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Leptin* b (ng/ml)</td>
<td>3.22 (2.63 to 3.95)</td>
<td>5.05 (4.33 to 5.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP* c (mg/l)</td>
<td>0.43 (0.30 to 0.58)</td>
<td>0.60 (0.46 to 0.77)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* values are back-transformed means and 95%CI of log data

a boys n=116, girls n=94
b boys n=115, girls n=93
c boys n=111, girls n=91
Table 2 – Associations between objectively-measured physical activity (5-8y) and metabolic markers at 8y: partial correlation (p)

<table>
<thead>
<tr>
<th>Metabolic risk factors</th>
<th>Model</th>
<th>All*</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total PA</td>
<td>MVPA (mins)</td>
<td>Total PA</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Model 1</td>
<td>-0.06 (0.46)</td>
<td>-0.07 (0.33)</td>
<td>-0.06 (0.56)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>-0.01 (0.88)</td>
<td>0.00 (0.98)</td>
<td>-0.02 (0.85)</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Model 1</td>
<td>-0.17 (0.02)</td>
<td>-0.17 (0.02)</td>
<td>-0.14 (0.16)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>-0.20 (0.01)</td>
<td>-0.20 (0.01)</td>
<td>-0.14 (0.16)</td>
</tr>
<tr>
<td>Leptin</td>
<td>Model 1</td>
<td>-0.06 (0.38)</td>
<td>-0.04 (0.56)</td>
<td>-0.01 (0.96)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>0.00 (0.96)</td>
<td>+0.02 (0.64)</td>
<td>+0.02 (0.77)</td>
</tr>
<tr>
<td>hs CRP</td>
<td>Model 1</td>
<td>-0.03 (0.71)</td>
<td>-0.02 (0.80)</td>
<td>-0.11 (0.30)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>-0.01 (0.93)</td>
<td>+0.01 (0.91)</td>
<td>-0.12 (0.24)</td>
</tr>
</tbody>
</table>

* controlled for gender
Model 1 – controlled for age, seasonality and between-Actigraph variation
Model 2 – as Model 1 with further adjustment for diet and %body fat
Figure 1 - Insulin resistance and adiponectin by tertiles of physical activity

* p<0.01 for ‘least vs mid active’ and ‘least vs most active’