Sex differences in resting energy expenditure and their relation to insulin resistance in children (EarlyBird 13)¹–³

Jo Kirkby, Brad S Metcalf, Alison N Jeffery, Christina F O’Riordan, Jenny Perkins, Linda D Voss, and Terence J Wilkin

ABSTRACT

Background: Insulin resistance is believed to be the process underlying type 2 diabetes and premature cardiovascular disease. We have established that a relation between body mass and insulin resistance calculated by homeostasis model assessment (HOMA-IR) exists by 5 y of age in contemporary UK children. Resting energy expenditure (REE) is variable among individuals and is one of many factors controlling body mass.

Objective: The objective was to investigate the relations between REE, body mass, and HOMA-IR in young children.

Design: EarlyBird is a nonintervention prospective cohort study of 307 healthy 5-y-olds that asks the question: Which children develop insulin resistance and why? REE by indirect calorimetry and HOMA-IR were measured in addition to total body mass, fat-free mass (FFM) by biometry, body mass index (BMI; in kg/m²), and skinfold thickness when the mean age of the cohort was 5.9 ± 0.2 y.

Results: Whereas the BMI of the boys was lower than that of the girls (x ± SD: boys, 15.9 ± 1.9; girls, 16.5 ± 1.9; P = 0.03), their REE was higher by 6% (x ± SD: 472 ± 615 compared with 469 ± 31 kJ/d; P = 0.002). This difference persisted after adjustment for FFM and other anthropometric variables (P = 0.04). In boys, there was a weak, although significant, inverse correlation between REE and HOMA-IR, independent of fat mass and FFM (boys: r = −0.21, P = 0.03; girls: r = 0.12, P = 0.34).

Conclusion: There is a sex difference in REE at 6 y of age that cannot be explained by body composition. The difference appears to be intrinsic, and its contribution to sex differences in adiposity and HOMA-IR in children merits further exploration.


KEY WORDS REE, insulin resistance, sex difference, metabolic syndrome, childhood

INTRODUCTION

The prevalence of obesity is rising across all age groups (1). It is also of concern that type 2 diabetes, which was previously seen only in adults, is presenting increasingly in adolescents and even younger children (2). Obesity is associated with insulin resistance, which is known to be an important threat to adult health, and is believed to underlie type 2 diabetes and premature cardiovascular disease (3). However, insulin resistance can precede the onset of diabetes by several years and can be acquired early in life, when it is potentially reversible.

The maintenance of weight is the result of a long-term balance between energy intake and expenditure. A variance in the direction of intake as small as 2% can lead to obesity (4). Obesity is a multifactorial problem, but there is conflicting evidence about the roles of resting energy expenditure (REE) and physical activity in its development (5). REE is variable among individuals and is the largest component of energy expenditure, comprising 60–80% of the total. As such, REE is one of the many factors that could influence weight and thereby modulate insulin resistance. Blonk et al (6) found REE to be an independent determinant of insulin sensitivity in adults with type 2 diabetes. Little, however, is known of these relations in healthy young children.

The determinants of REE are well established in adults. Aerobic activity and resistance training are reported to influence REE (7) as is dietary composition (8). Birth weight was recently reported by Eriksson et al (9) to correlate inversely with energy expenditure. There is also a genetic component (10), but fat-free mass (FFM) remains the principal determinant of REE across all age ranges. The organs (eg, digestive tract, kidney, lungs, heart, brain) together contribute around 60% to the energy expended by fat-free tissue, and muscle is responsible for the remaining 40% (11). REE was shown to be significantly higher in adult men than in women, by an average 209 kJ/d, irrespective of differences in body composition and aerobic fitness (12, 13).

A sex difference in REE was also reported in prepubertal children (14). However, inadequate sample sizes or inappropriate methodology often limit REE studies in young children (15, 16). When sex differences were found, their implications were not explored, and there is little research about the contribution of REE to insulin resistance independent of body composition. Previous studies have consistently shown that estimation equations for energy expenditure on the basis of weight are unreliable (17–19) and that measures of REE are preferable. Indirect calorimetry was previously shown to be reproducible in children (20) and is used in the present study.

Girls are intrinsically more insulin resistant than boys (21), and in this study we determined the contribution of REE to the homeostasis model assessment for insulin resistance (HOMA-IR),...
independently of body composition. Girls also carry more body fat than boys from birth, so we examined the relation of sex to REE as a possible explanation.

SUBJECTS AND METHODS

EarlyBird is a nonintervention prospective cohort study of healthy school entrants (age: 4.9 y) in the city of Plymouth, United Kingdom, which began in the year 2000. It is designed to last 12 y and to address the question: Which children become insulin resistant, and why? All 67 Plymouth primary schools were identified, and their head teachers were asked for agreement to participate in the study. Fifty-four schools agreed and were stratified into quartiles according to the proportion of children entitled to free school meals, a socioeconomic proxy. A random selection was made from each quartile, and registration for the study was invited during school induction meetings when parents expressing interest were given a full explanation. With parents' written consent and children’s assent, a total of 307 children (137 girls, 170 boys) who started school between January 2000 and January 2001 have become the EarlyBird cohort. S&SW Devon Local Research Ethics Committee gave ethical approval in the summer of 1999.

Measures were made at recruitment and 12 mo later of height, weight, body mass index (BMI), skinfold thickness at 5 sites (triceps, biceps, subscapular, suprailliac, and umbilical), and circumference of midarm, hip, and waist. A fasting blood sample was taken, and insulin resistance was calculated from insulin and glucose measures with use of HOMA (22). HOMA is widely used in children, but it cannot be validated directly with the gold-standard reference of hyperinsulinemic and euglycemic clamp in healthy children for ethical reasons. Comparison with clamp in adults, however, reveals a correlation of 0.75 (22). Although the BMI of boys being 6.7% higher than that of the girls (4732 compared with 4435 kJ/d, respectively, P = 0.04). It is generally assumed that the relations between energy expenditure and fat mass, which is not considered to contribute significantly to energy

Statistics

SPSS for Windows was used for statistical analysis (version 10.1.3; SPSS Inc, Chicago). HOMA-IR was not distributed normally and was, therefore, log transformed before analysis. Means, SD, and 95% CIs were calculated for all main outcome measures. Pearson product moment correlation coefficients were used to quantify relations between the variables and partial correlations to quantify independent effects. Manual backward elimination regression was used to elucidate the significant independent determinants of REE and HOMA-IR. Analysis of variance was used for sex comparisons on all main outcome measures. Analysis of covariance was used to analyze the sex difference in REE. The 5% significance level was used for all hypothesis testing.

RESULTS

Presented here are the results from the 12-mo visit (age: 5.9 ± 0.2 y). Of the original 307 children who joined the study, 18 had withdrawn or moved away from the area. Of the remaining 289 children, 25 did not undergo REE measurement for various reasons (21 missed through illness, and 2 declined the hood). Nineteen children tolerated the hood for fewer than 10 min and were excluded from the analysis. A further 41 measurements failed to meet the calibration specification (inspired O2 value outside the specified range of 20.90–20.99%). Accordingly, 204 analyses of REE (66% of the children originally recruited) are included in this report. One hundred forty-five children also had a valid baseline measure for calculation of year-on-year reproducibility. Compliance rates in the other studies are indicated alongside the corresponding data.

Year-on-year correlations (baseline compared with 12-mo visit) for all main outcome measures were high, confirming the techniques as robust (Table 1). The simple outcome measures (12-mo visit) are shown in Table 2. Although the BMI of boys was significantly lower, their REE was significantly higher than that of the girls. The measures of fat mass with use of bioelectrical impedance were not significantly different between boys and girls. There were strong relations, as anticipated, between REE and all anthropometric measures (Table 3). Even after adjustment for anthropometric variables, however, the sex difference in REE between boys and girls remained; the mean value in the boys being 6.7% higher than that of the girls (4732 compared with 4435 kJ/d, respectively, P = 0.04). It is generally assumed that the relations between energy expenditure and fat mass, which is not considered to contribute significantly to energy

Nutren Technology Ltd, Manchester, United Kingdom (28). Performance tests reportedly show a mean error of 0.3% ± 2% in the measurement of oxygen consumption and 1.8% ± 1% in that of carbon dioxide production (28). The children were in a fasting state overnight and were measured at around 0900. They were given a 5-min settling-in period under the hood before data collection for a minimum of 10 min, usually 15 min. Throughout measurement, the children were encouraged to lie quietly, and they watched a nonviolent video. Use of a video was previously shown to minimize minute-to-minute variation of REE as a result of excessive fidgeting (29). Any 1-min interval in which the recorded REE was ±2 SD of the child’s overall mean was ignored. An observer made notes during the period of measurement, and such aberrations in the recording were almost always the result of sneezing, coughing, or talking.
TABLE 1
Year-on-year correlations for outcome measures

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>283</td>
<td>0.96 (0.95, 0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>284</td>
<td>0.90 (0.88, 0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sum of skinfold thicknesses</td>
<td>277</td>
<td>0.84 (0.80, 0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity</td>
<td>226</td>
<td>0.49 (0.38, 0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>REE</td>
<td>145</td>
<td>0.49 (0.36, 0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>269</td>
<td>0.44 (0.34, 0.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Shown are the Pearson correlations (with 95% CIs) between measurements made at baseline and those made at the 12-mo visit. REE, resting energy expenditure; HOMA-IR, homeostasis model assessment for insulin resistance (22).

TABLE 2
Summary of main outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE (kJ/d)</td>
<td>4724 ± 615 (4611, 4837)</td>
<td>4469 ± 531 (4351, 4586)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.63 ± 0.51 (0.53, 0.72)</td>
<td>0.87 ± 0.63 (0.75, 1.03)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.35 ± 0.47 (3.46, 3.64)</td>
<td>3.47 ± 0.49 (3.36, 3.58)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21.9 ± 4.0 (21.2, 22.6)</td>
<td>22.3 ± 4.4 (21.3, 23.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.9 ± 1.9 (15.6, 16.3)</td>
<td>16.6 ± 1.9 (16.1, 17.0)</td>
</tr>
<tr>
<td>Sum of skinfold thicknesses (cm)</td>
<td>4.1 ± 1.6 (3.8, 4.4)</td>
<td>5.2 ± 1.9 (4.7, 5.6)</td>
</tr>
<tr>
<td>Midarm circumference (cm)</td>
<td>17.5 ± 1.8 (17.1, 17.8)</td>
<td>18.2 ± 1.7 (17.8, 18.6)</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>60.4 ± 4.7 (59.5, 61.2)</td>
<td>62.0 ± 5.4 (60.8, 63.1)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>52.7 ± 4.1 (51.9, 53.4)</td>
<td>52.7 ± 4.8 (51.7, 53.8)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>0.39 ± 1.7 (3.5, 4.2)</td>
<td>3.9 ± 2.9 (3.3, 4.5)</td>
</tr>
<tr>
<td>Fat percentage (%)</td>
<td>17.0 ± 4.3 (16.2, 17.8)</td>
<td>16.1 ± 4.4 (14.5, 17.7)</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>18.2 ± 2.7 (17.7, 18.7)</td>
<td>18.7 ± 2.1 (18.2, 19.2)</td>
</tr>
</tbody>
</table>

All values are x ± SD; 95% CI in parentheses. REE, resting energy expenditure; HOMA-IR, homeostasis model assessment for insulin resistance (22).

1. All values are x ± SD; 95% CI in parentheses. REE, resting energy expenditure; HOMA-IR, homeostasis model assessment for insulin resistance (22).

2. Significantly different from boys (one-way ANOVA): 2 P < 0.01, 3 P < 0.05, 4 P < 0.001.

The combination of FFM and midarm and hip circumferences best predicted REE in the boys, together explaining 49% of the variation. The regression equation was as follows:

REE (boys) = 605 + (FFM × 36.5) + (midarm × 43.5) + (hip × 14.8) (1)

In the girls, fat mass, FFM, and hip circumference explained 57% of the variation in REE. The regression equation was as follows:

REE (girls) = 1229 + (FM × 41.3) + (FFM × 32.2) + (midarm × 38.9) + (hip × 18.2) (2)

Overall, the following model best predicted REE in boys and girls, explaining 52% of the variation:

REE = 1255 + (FFM × 43.0) + (sex × FM × 11.3) + (sex × FFM × 13.5) + (sex × midarm × 32.2) + (sex × hip × 18.2) (3)

where girls = 0 and boys = 1.

Physical activity and dietary composition data are presented in Table 4, and correlations between these variables and REE are presented in Table 5. By comparing the mean amount of physical activity undertaken at the 3 different levels (in Subjects and methods), boys tended to take less low-intensity physical activity and undertook significantly more high-intensity activity than the girls, but no component of physical activity could explain the sex difference in REE. There were no statistically significant correlations between REE and any intensity of physical activity in the boys. There were weak, but significant, correlations between physical activity and REE in the girls that increased when fat mass and FFM were accounted for. There were no significant sex differences in dietary choices, and no component of dietary composition appeared to influence REE independently of fat and FFM (P ≥ 0.5).
There was a positive correlation between REE and birth weight in both girls and boys across the range (Table 6). Birth weight also correlated positively with FFM in both sexes (boys: \( r = 0.44, P < 0.001 \); girls: \( r = 0.38, P = 0.001 \)) but did not correlate with REE independently of FFM.

A modest but significant correlation was found between HOMA-IR and REE in the girls that was lost on adjustment for tissue mass (Table 7). However, a small and statistically significant negative relation appeared in the boys on adjusting for tissue mass (\( \text{HOMA-IR} \) and \( \text{REE} \) in the girls). The combination of fat mass and \( \text{REE} \) best predicted weight when all but one of the analyses were made. The one exception was the year-on-year correlation between month 12 and month 0, when only 145 measures were available. All other outcome measures were available at month 12 in the 204 children for whom the \( \text{REE} \) measurement was valid, and the results of this study remained unchanged when all analyses were confined to these children alone.

**DISCUSSION**

We have shown that the \( \text{REE} \) of boys at 6 y is a mean 260 kJ/d, some 6.7%, higher than that of girls, even after adjustment for sex differences in anthropometry, physical activity, and dietary composition. This difference is sizable in relation to the small variations in energy balance, which is known to lead to obesity in the long term (4). Values reported here for \( \text{REE} \) in the children in the EarlyBird study as a whole are consistent with values previously noted in children of a similar age (14, 17), but sex differences were not noted before, and their relation to anthropometry, body composition, food choices, and physical activity were not explored.

In elderly individuals, the higher \( \text{REE} \) reported among men is thought to be partially explained by higher levels of sympathetic activity.

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**TABLE 4**

<table>
<thead>
<tr>
<th>Physical activity, ( n = 100 ) boys, 76 girls (( \times 10^5 ) units/wk)(^2)</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intensity</td>
<td>10.0 ± 1.3 (9.7, 10.2)</td>
<td>10.3 ± 1.1 (10.1, 10.6)</td>
</tr>
<tr>
<td>Moderate intensity</td>
<td>15.0 ± 3.2 (14.4, 15.6)</td>
<td>14.4 ± 2.7 (13.8, 14.8)</td>
</tr>
<tr>
<td>High intensity</td>
<td>13.4 ± 7.4 (12.0, 14.9)</td>
<td>11.3 ± 4.7 (10.3, 12.4)(^1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary composition, ( n = 113 ) boys, 82 girls (%)(^3)</th>
<th>Fat</th>
<th>Fiber</th>
<th>Carbohydrate</th>
<th>Sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>31.8 ± 8.1 (30.3, 33.4)</td>
<td>29.3 ± 11.5 (27.2, 31.5)</td>
<td>40.4 ± 7.7 (39.0, 41.8)</td>
<td>51.3 ± 16.0 (48.3, 54.3)</td>
</tr>
<tr>
<td>Boys</td>
<td>31.8 ± 10.4 (29.5, 34.1)</td>
<td>29.3 ± 11.5 (27.2, 31.5)</td>
<td>39.8 ± 9.4 (37.7, 41.9)</td>
<td>49.6 ± 18.9 (45.5, 53.8)</td>
</tr>
</tbody>
</table>

\(^1\) All values are \( \bar{x} \pm SD \); 95% CI in parentheses.

\(^2\) Low, moderate, and high intensity correspond to activity levels achieved by sitting, walking, and running, respectively.

\(^3\) Significantly different from boys, \( P = 0.03 \) (one-way ANOVA).

\(^4\) Food components by food-frequency questionnaire, eg, fiber percentage is the frequency of high-fiber foods eaten by the child, expressed as a proportion of the maximum frequency of high-fiber foods obtainable from the questionnaire.

---

**TABLE 5**

<table>
<thead>
<tr>
<th>Intensity of physical activity</th>
<th>Correlation Boys (( n = 100 ))</th>
<th>Correlation Girls (( n = 76 ))</th>
<th>Partial correlation Boys (( n = 90 ))</th>
<th>Partial correlation Girls (( n = 65 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>( -0.02 (-0.22, 0.18) )</td>
<td>( 0.02 (-0.21, 0.24) )</td>
<td>( 0.10 (-0.11, 0.30) )</td>
<td>( 0.11 (-0.14, 0.35) )</td>
</tr>
<tr>
<td>Moderate</td>
<td>( 0.83 )</td>
<td>( 0.89 )</td>
<td>( 0.35 )</td>
<td>( 0.39 )</td>
</tr>
<tr>
<td>Moderate</td>
<td>( 0.09 (-0.11, 0.28) )</td>
<td>( 0.13 (-0.10, 0.35) )</td>
<td>( 0.17 (-0.04, 0.36) )</td>
<td>( 0.33 (0.09, 0.53) )</td>
</tr>
<tr>
<td>High</td>
<td>( 0.40 )</td>
<td>( 0.26 )</td>
<td>( 0.11 )</td>
<td>( 0.008 )</td>
</tr>
<tr>
<td>High</td>
<td>( 0.15 (-0.05, 0.34) )</td>
<td>( 0.23 (0.005, 0.43) )</td>
<td>( 0.005 (-0.20, 0.21) )</td>
<td>( 0.30 (0.06, 0.51) )</td>
</tr>
<tr>
<td>Total</td>
<td>( 0.13 )</td>
<td>( 0.05 )</td>
<td>( 0.97 )</td>
<td>( 0.02 )</td>
</tr>
</tbody>
</table>

\(^5\) Shown are the Pearson correlations with 95% CIs or the partial correlations with 95% CIs (controlled for fat mass and fat-free mass). Low, moderate, and high intensity correspond to activity levels achieved by sitting, walking, and running, respectively.
nervous system activity (30). In younger adults, it was suggested that the greater thermogenic effect of androgens compared with estrogens might also contribute to the sex difference (12, 13). Goran et al (14) investigated the determinants of REE in prepubertal children aged between 3.9 and 7.3 y and likewise found an independent effect of sex on REE. However, the REE measurements in that study were not carried out in the fasting state and inevitably incorporated the unpredictable energy cost of meal-induced thermogenesis. The children in the EarlyBird study were in a fasting state for at least 10 h, minimizing this effect. Nevertheless, the data are consistent, and the reported differences in sex steroid profiles among prepubertal children, albeit small (31), might still contribute to the sex differences in REE that we describe here.

Dietary composition was shown to affect REE (8) and was assessed here by food-frequency questionnaire. No food component in the present study was significantly associated with REE independently of fat mass and FFM. Nor could physical activity explain the sex difference in REE, although boys were significantly more active than the girls. A correlation between physical activity and REE was only observed in girls after controlling for fat mass and FFM.

No correlation was found between birth weight and REE after adjustment for current FFM by partial correlation. This finding is in contrast with that of Weyer et al (32) who found a negative correlation between birth weight and sleeping metabolic rate. The discrepancy might be explained in part by the different populations under investigation. Weyer et al (32) studied adult Pima Indians, whereas EarlyBird is a cohort of young, white 6-y-olds. Recent work by Eriksson et al (9) also reported a negative correlation in adults between birth weight and REE per kilogram of FFM. However, standardizing REE in this way needs to be interpreted with caution (33), because it was shown that the ratio of REE per kilogram of FFM:FFM is not constant (34). We can confirm that, although the 2 are correlated at the age of 6 y, their ratio decreases with increasing FFM ($r = -0.45, P < 0.001$).

A limitation of many studies on REE in children is their small sample size, exacerbated when comparing subgroups. Small differences or correlations missed for lack of statistical power are important because variations in REE of clinical relevance need only be small to have a substantial effect on energy balance over a period of time. Earlier studies that were unable to demonstrate a sex difference in REE were smaller and probably underpowered (15, 16, 34). The sample size used here provided the study with 87% power to detect the observed sex difference in REE at the 5% significance level.

Obesity results from sustained positive energy balance and an excess of as little as 105 kJ/d can result in excess weight gain. A low REE for a given body weight is likely to predispose to obesity (35–37), although no data are available for children. The prevalence of obesity is known to be lower in white than in black women (38), and it was suggested that the higher REE observed in the white women is responsible (39). The sex difference in REE that we observed might, therefore, predispose girls to obesity more than the boys, and the obesity epidemic is known to be affecting girls more than boys (40). Furthermore, as we noted earlier, prepubertal girls are intrinsically more insulin resistant than boys (21).

We have demonstrated a weak negative correlation between REE and HOMA-IR in boys but not girls in the United Kingdom. This correlation was independent of both fat mass and FFM. These data are consistent with those of Blonk et al (6) who investigated the determinants of insulin sensitivity in adults with type 2 diabetes with use of the euglycemic clamp technique. They found that percentage fat and REE were the main determinants of insulin sensitivity in men and together explained 44% of the variation. Insulin resistance is thought to be influenced by cardiorespiratory fitness levels in adults. However, fitness and physical activity are poorly correlated, and we found no association in the boys of the EarlyBird study either between physical activity and REE or between physical activity and HOMA-IR. REE thus appears to have an independent, albeit modest, relation to HOMA-IR in boys at aged 6 y and, together with fat mass, explained 11% of the variation in their HOMA-IR.

In conclusion, we found that boys as young as 6 y have an intrinsically higher REE than girls and that REE is an independent (inverse) determinant of HOMA-IR in boys. The findings could have important implications for weight gain and insulin resistance as children grow and mature.

The paper was jointly written by all the authors, and all took part in the study design. TJW had the original idea and is guarantor for the EarlyBird study. LDV is study coordinator. JK was responsible for the data analysis and writing the manuscript. BSM provided statistical consultation for data analysis. ANJ and JP were responsible for collection of the data, and CO’R was responsible for interpretation and analysis of the food frequency questionnaires. None of the authors had any conflicts of interest.

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