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Original Article

Contrasting longitudinal and cross-sectional relationships between insulin resistance and percentage of body fat, fitness, and physical activity in children—the LOOK study

Telford RD, Cunningham RB, Shaw JE, Dunstan DW, Lafferty ARA, Reynolds GJ, Hickman PE, Southcott E, Potter JM, Waring P, Telford RM. Contrasting longitudinal and cross-sectional relationships between insulin resistance and percentage of body fat, fitness and physical activity in children- the LOOK study.
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Background: Knowledge of individual changes in insulin resistance (IR) and longitudinal relationships of IR with lifestyle-associated factors are of important practical significance, but little longitudinal data exist in asymptomatic children. We aimed to determine (a) changes in the homeostatic model of insulin resistance (HOMA-IR) over a 2-yr period and (b) comparisons of longitudinal and cross-sectional relationships between HOMA-IR and lifestyle-related risk factors.
Methods: Our subjects, 241 boys and 257 girls, were assessed at age 8.1 yr (SD 0.35) and again 2 yr later for fasting blood glucose and insulin, dual X-ray absorptiometry-assessed percentage of body fat (%BF), pedometer-assessed physical activity (PA), and cardio-respiratory fitness (CRF) by multistage running test.
Results: HOMA-IR was initially 9% greater in girls than boys and 27% greater 2 yr later. There was no evidence of longitudinal relationships between HOMA-IR and %BF in boys or girls, despite significant cross-sectional relationships ($p < 0.001$). In boys, there was evidence of a longitudinal relationship between HOMA-IR and both PA ($p < 0.001$) and CRF ($p = 0.05$). In girls, we found a cross-sectional relationship between HOMA-IR and CRF ($p < 0.001$).
Conclusions: HOMA-IR increases between 8 and 10 yr of age and to a greater extent in girls. Longitudinal, unlike cross-sectional, relationships do not support the premise that body fat has any impact on HOMA-IR during this period or that PA or CRF changes affect HOMA-IR in girls. These data draw attention to difficulties in interpreting observational studies in young children.

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Key words: IR – children – PA – body fat – obesity – fitness

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Conflict of interest

None of the authors have any conflict of interest or financial associations with any aspect of this study.

Knowledge of how blood bio-markers change with age and understanding the relationships of bio-markers with lifestyle factors are important components of preventative medicine. This is certainly true in relation to children and their risk of developing type 2 diabetes. Insulin resistance (IR) is a precursor and risk factor for type 2 diabetes (1), and the homeostasis model homeostatic model of insulin resistance (HOMA-IR) is a widely used measure in children (2–4). While measurement of fasting insulin alone may produce similar findings to HOMA-IR in asymptomatic subjects, the inclusion of glucose in estimating HOMA-IR becomes important in longitudinal studies where subjects may develop clinical signs of IR (5). Consequently, knowledge of how HOMA-IR changes with age in healthy children and the relationships of lifestyle-modifiable characteristics with changes in HOMA-IR should be fundamental to the provision of advice directed at preventing type 2 diabetes. However, such knowledge, only well provided by longitudinal studies, is lacking.

Physical activity (PA), cardio-respiratory fitness (CRF), and percentage of body fat (%BF) are all known to be associated with risk of developing type 2 diabetes, and cross-sectional studies have identified relationships between these variables in children (6). However, cross-sectional studies, unlike longitudinal studies, cannot distinguish differences between children from changes within children over time and Fig. 1 illustrates how cross-sectional and longitudinal data may generate distinctly different relationships. Prior to recent longitudinal work by the Early Bird study group measuring IR, among other factors, in children between the ages of 5 and 8 yr (2, 3, 7), little or no work had been done in this area (3).

Therefore, to extend the current knowledge of preventative medicine in children, we set out to answer the following questions. (a) Are changes in IR over the 2-yr interval between 8 and 10 yr of age associated with changes in PA, CRF, or %BF? (b) Do relationships between IR and PA, CRF, and %BF differ between boys and girls? (c) Does IR increase or decrease from the age of 8 to 10 yr old? (d) Is the change in IR different in boys and girls? (e) Can we make any inferences as to how the lifestyle of 8- to 10-yr olds may contribute to better metabolic control?

Methods

Subjects

Our subjects were 241 boys and 257 girls, participants in the Lifestyle of our Kids (LOOK) study as previously described (8), recruited from 30 government-funded primary schools in Canberra, Australia, where overall median taxable family income closely approximated the national average. The characteristics of the group are summarized in Table 1. Approximately 90% of the children had one or both parents of Caucasian descent, 7% of Asian descent, 1% of Indigenous Australian or Polynesian, and we had no data on 2% of the families.

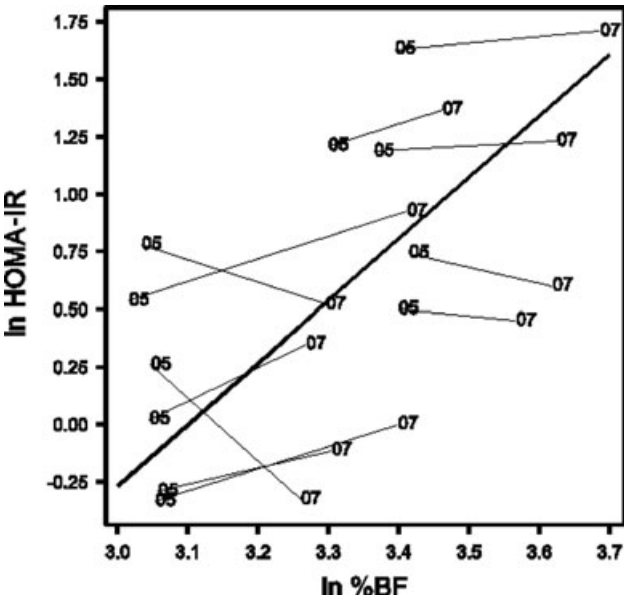

Fig. 1. Schematic illustration showing how longitudinal data allow separation of within-child and between-children effects and how these relationships may differ. Using selected data points from our study, the slender lines show *non-significant* within-child (longitudinal) relationships from 2005 to 2007 and the solid line shows a *significant* between-children (cross-sectional) relationship.

Measurements

Height was measured by a portable stadiometer to the nearest 0.001 m and body mass by portable electronic scales to the nearest 0.05 kg. Body composition was measured using dual x-ray absorptiometry (DXA, Hologic Discovery QDR Series, Hologic Inc., Bedford, MA, USA) and QDR Hologic Software Version 12.4:7 was used to generate fat mass and %BF calculation.

Fasting blood samples were collected before school in separation tubes and serum samples were mixed and allowed to clot for up to 30 min prior to centrifugation. Samples were centrifuged for 10 min at 2850 rpm (Spintron GT-25P, Spintron Pty Ltd, Melbourne, Australia) and either immediately frozen in dry ice and stored at -80 deg C for subsequent analysis or taken to ACT Pathology, The Canberra Hospital for analysis. Care was taken to maximize consistency of laboratory handling of samples, procedures were carried out according to instrument manufacturers' standards, and biochemical analysis was performed

Table 1. Characteristic of subjects

	2005		2007	
	Girls (n = 257)	Boys (n = 241)	Girls (n = 257)	Boys (n = 241)
Age (yr)	8.09 (0.35)	8.1 (0.34)	10.1	10.1
Height (cm)	130.3 (5.6)	131.7 (6.3)	140.7 (8.2)	141.7 (6.7)
Mass (kg)	29.6 (6.2)	29.6 (6.2)	37.5 (11.2)	36.6 (7.4)
Body mass index (kg/m^2)	17.3 (2.8) (12.7–27.2)	17.0 (2.4) (12.5–28.2)	18.5 (3.2) (12.7–31.1)	18.1 (2.7) (13.9–28.4)

Values listed are means and SD at test 1 (2005) and test 2 (2007).

within acceptable limits of internal quality control. Glucose concentration (GLU) was measured by hexokinase colorimetric methodology on the Architect Ci8200 (Abbott laboratories, IL 60064, USA). Insulin concentration (INS) was measured using microparticle enzyme immunoassay on the AXSYM (Abbott laboratories, IL 60064, USA).

Our marker of choice (primary outcome) was the HOMA-IR, (9) where HOMA-IR = [fasting INS (mU/L) × fasting GLU (mmol/L)]/22.5. While insulin sensitivity may be a more appropriate term in asymptomatic children, HOMA-IR is validated for use with children (10, 11) and consistent with recent publications on children (3, 4, 7).

The 20 m shuttle run was used to estimate CRF, being well established as a field test with children (12). To measure PA, children wore pedometers on their hip for seven consecutive days, the first day's measurements being ignored on the premise that the novelty of wearing the pedometers may influence the initial activity of our 8-yr olds. The pedometers were Walk 4 Life (Plainfield, IL, USA) sealed pedometers, recommended for use with children (1).

A parent-assisted child self-assessment was employed to assess the Tanner stages of development (13) questionnaire and diagrams similar to those used previously (14).

Measurements of PA, CRF, and blood collections were completed over two 12-wk periods beginning in October 2005 and October 2007. About 95% of the DXA measures were also completed at these stages but some missed appointments were rescheduled after this period. The heights and weights listed in Table 1 are those taken at the time of the DXA measurements.

Statistical treatments

As our data are longitudinal, the response variable HOMA-IR varies at two levels, between-children and within-child, as do the candidate explanatory variables, PA, CRF, and %BF. PA for each year was derived from repeated pedometer observations taking into account possible differences in activity, day of week, and weekend. The measure chosen to maximize use of data, and because of its desirable statistical properties, was the best linear unbiased predictor (15). HOMA-IR was transformed by natural logarithm to satisfy distributional and variance assumptions, while explanatory variables PA and CRF were scaled by square roots and %BF by natural logarithms to better meet linearity assumptions. Our longitudinal data allow us to measure the difference in the response (HOMA-IR) across individuals who differ by 1 unit in a given explanatory variable (e.g., PA), as well as the expected change in the response over time per unit change in the explanatory variable. To distinguish these effects, we undertook two analyses—one for the average between-children response (using each of the 2 yr) and the other for the change in response in each individual over the 2 yr. Our statistical model takes the form

IR = constant + sex ×child random effect + effect due to age + effect due to PA + sex × PA interaction effect + within-child random error

This model fits within the general framework of general linear mixed modeling (15). Restricted maximum likelihood is used to estimate variance components and weighted least squares for estimating fixed effects. Statistical significance of effects was assessed by calculating adjusted Wald statistics (16). General model checking procedures were routinely used to identify aberrant data and to check the model assumptions.

This study in its entirety was approved by the Australian Capital Territory Health and Community Care Human Research Ethics Committee.

Results

As indicated in Table 2, the girls were measured with higher mean HOMA-IR values than the boys, the boys being generally more physically active with better CRF, and the %BF of the girls being greater than that of the boys. These differences were consistent across both test periods at mean ages 8 and 10 yr and all were significant with $p < 0.001$. During the 2 yr, there were significant increases in INS, GLU, and HOMA-IR

Table 2. Means and SD of variables

	2005		2007	
	Girls	Boys	Girls	Boys
Insulin (mU/L)	5.8 (3.4)	5.1 (2.7)	8.3 (4.5)	6.5 (3.7)
Glucose (mmol/L)	4.6 (0.43)	4.7 (0.47)	5.05 (0.38)	5.1 (0.34)
Homeostatic model of insulin resistance (HOMA-IR)	1.2 (0.79)	1.1 (0.59)	1.9 (1.1)	1.5 (0.88)
Percentage of body fat	27.8 (6.5)	22.7 (5.9)	28.7 (6.8)	24.5 (6.5)
Cardio-respiratory fitness (stages achieved)	3.5 (1.15)	4.2 (1.43)	4.5 (1.47)	5.5 (1.78)
Physical activity (PA) index ($\sqrt{}$steps per day)	98.5 (9.0)	108.1 (9.3)	94.0 (9.8)	102.5 (11.1)

Differences between the 2005 and 2007 results were significant in all cases [all $p < 0.001$ except for PA ($p < 0.01$)]. Gender differences in the means of 2005 and 2007 values were significant in all cases [$p < 0.001$ except for glucose ($p < 0.04$)]. The PA index is approximately equal to the square root of the mean number of steps per day.

Table 3. Percentiles of blood concentrations of glucose, insulin, and HOMA-IR at the two testing periods, 2005 and 2007

	Girls					Boys				
	5.0%	25.0%	Median	75.0%	95.0%	5.0%	25.0%	Median	75.0%	95.0%
HOMA-IR										
2005	0.50	0.72	1.04	1.52	2.51	0.40	0.71	0.98	1.35	1.92
2007	0.65	1.15	1.68	2.37	3.93	0.59	0.95	1.27	1.82	2.99
Glucose (mM/L)										
2005	4.00	4.40	4.60	4.90	5.40	3.93	4.40	4.70	4.90	5.58
2007	4.40	4.80	5.00	5.30	5.70	4.53	4.90	5.20	5.40	5.70
Insulin (mU/L)										
2005	2.44	3.58	5.10	7.20	11.20	2.03	3.40	4.70	6.30	8.78
2007	3.14	5.16	7.50	10.23	15.86	2.73	4.13	5.50	7.68	12.83

in both genders, these changes being accompanied in both boys and girls by significant increases in CRF, a reduction in PA, and a significant increase in %BF [all $p < 0.001$ except for PA ($p < 0.01$)].

Table 3 sets out the medians and percentiles for GLU, INS, and HOMA-IR with a view to contributing to the bank of reference data in asymptomatic children.

Figures 2–7 are graphical representations of the longitudinal and cross-sectional relationships between HOMA-IR and the functions of PA, CRF, and %BF.

There was no evidence of a longitudinal relationship between mean HOMA-IR and %BF in the boys or girls. Of the other longitudinal relationships with HOMA-IR in the boys, PA was significant ($p < 0.001$) with some weak evidence for CRF ($p = 0.05$). In the girls, however, we found no evidence that PA or CRF could explain variation in HOMA-IR.

Significant cross-sectional (between-children) relationships were found between HOMA-IR and %BF in both boys and girls ($p < 0.001$). These were accompanied by significant relationships between the means of HOMA-IR and CRF in the boys ($p = 0.02$) and the girls ($p < 0.001$). On the other hand, there was no evidence that PA was related to HOMA-IR on a cross-sectional basis for either boys or girls.

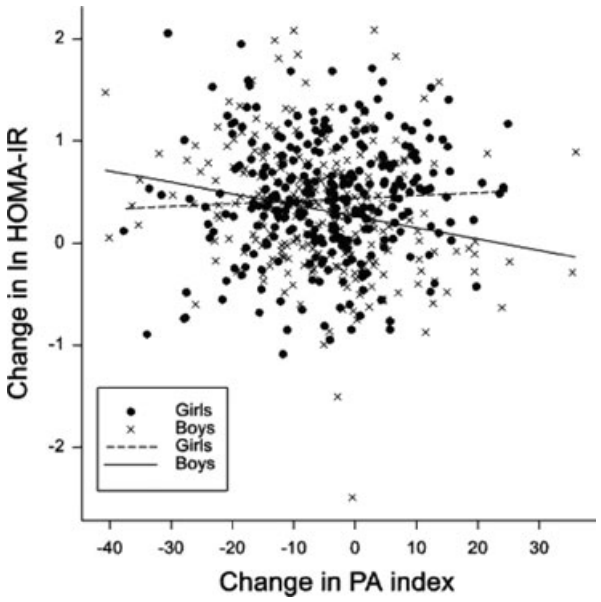

Fig. 2. Longitudinal (within-child) relationships between ln homeostatic model of insulin resistance (HOMA-IR) and the physical activity (PA) index with lines of best fit for boys ($p < 0.001$) and girls (not significant, $p = 0.37$).

About 64% of the boys and 66% of the girls completed the Tanner pubertal rating questionnaire following the

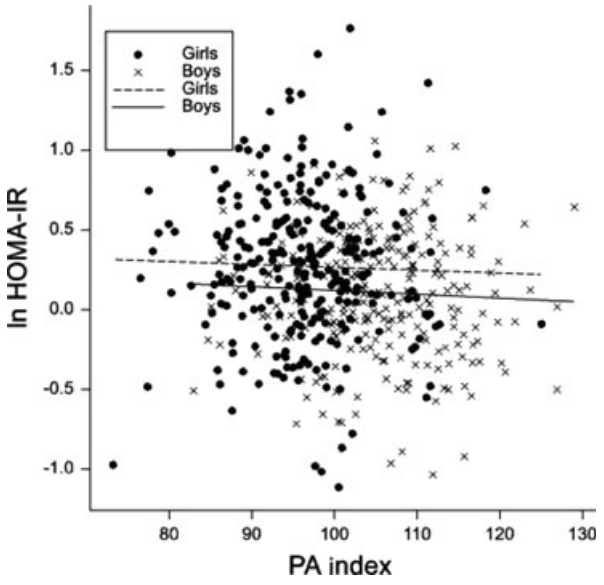

Fig. 3. Cross-sectional (between-children) relationship between ln HOMA-IR and the PA index with lines of best fit for boys (not significant, p = 0.42) and girls (not significant, p = 0.62).

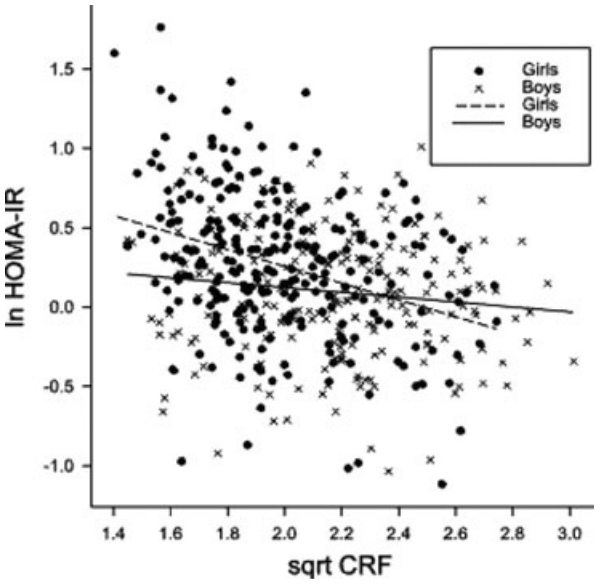

Fig. 5. Cross-sectional (between-children) relationship between ln HOMA-IR and CRF with lines of best fit for boys (p = 0.02) and girls (significant, p < 0.001).

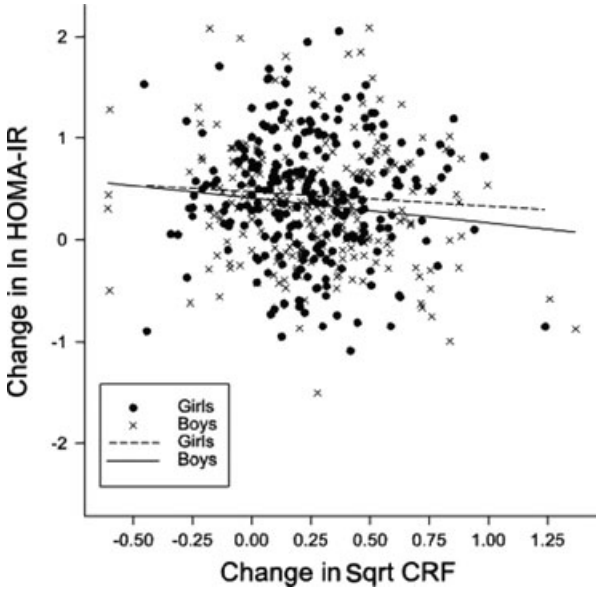

Fig. 4. Longitudinal (within-child) relationships between ln HOMA-IR and cardio-respiratory fitness (CRF) with lines of best fit for boys (p = 0.05) and girls (not significant, p = 0.31).

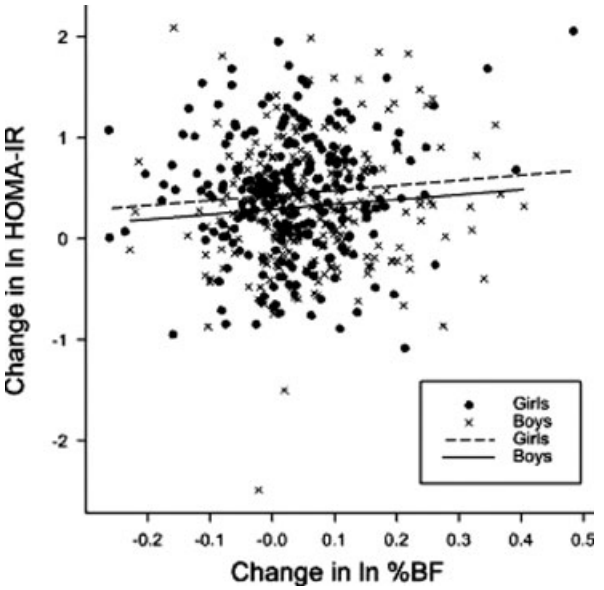

Fig. 6. Longitudinal (within-child) relationships between ln HOMA-IR and %BF with lines of best fit for boys (not significant, p = 0.19) and girls (not significant, p = 0.18).

assessments at age 10 (SD 0.3) yr. Using the assessments involving body hair development, 93% of the boys and 83% of the girls were prepubertal or early pubertal (stage 1 or 2). However, 17% of the girls reported breast development at stage 3 or 4 compared with 7% of the boys reporting genital development at stage 3 or 4, indicating that more of the girls had advanced into early puberty than the boys at the second testing phase. The change in HOMA-IR over the 2 yr was 1.13 for girls at Tanner stage 3 pubic hair compared with 0.37 and 0.38 at pubic hair Tanner stages 1 and 2, respectively, the difference in the ΔHOMA-IR (change in HOMA-IR) at stage 3 being significant (p = 0.03).

To investigate any potentially confounding effect of pubertal development on the relationships reported above, the relationships were recalculated with the exclusion of those children who had reached Tanner stage 2 or greater following the second measurement period. The recalculations did not change the nature of any of our relationships.

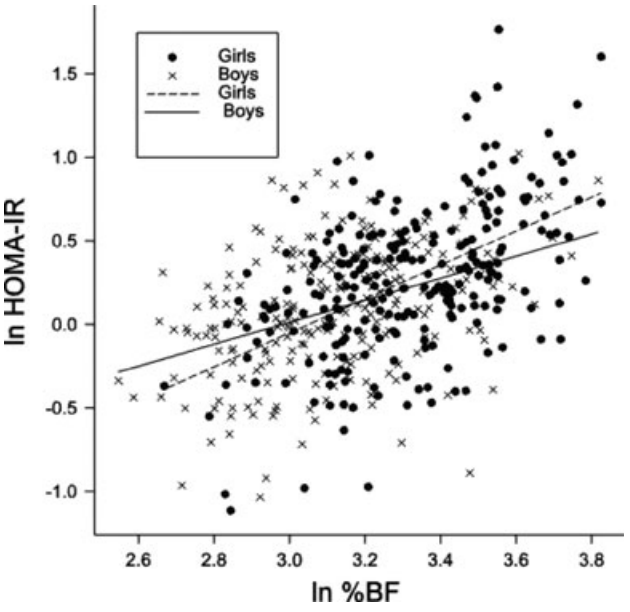

Fig. 7. Cross-sectional (between-children) relationship between ln HOMA-IR and percentage of body fat with lines of best fit for boys ($p < 0.001$) and girls ($p < 0.001$).

Discussion

The most important new finding in our study of predominantly prepubertal asymptomatic children was the discordance in the longitudinal and cross-sectional relationships between HOMA-IR and each of %BF, PA, and CRF. Specifically, we found (a) little evidence to suggest that changes in HOMA-IR between the ages of 8 and 10 were related to changes in %BF in either boys or girls and (b) increases in PA and CRF were associated with an attenuation of the general increase in HOMA-IR in the boys but not the girls. Furthermore, we showed that HOMA-IR increased between the ages of 8 and 10 yr in both boys and girls, with girls possessing not only greater absolute values of HOMA-IR at both age groups but also greater changes over the 2 yr. Our data complement previous cross-sectional findings of greater HOMA-IR in girls than in boys, both in 5-yr olds non-selected for obesity or illness (17) and in 8- to 10-yr olds classified as obese (18). The general increase in HOMA-IR in boys and girls as they progress from 8- to 10-yr old can be contrasted with previous Early Bird work (2, 7), in which HOMA-IR decreased between the ages of 5 and 7 yr (despite an increase in adiposity). We are confident of the accuracy of our blood results, as the sample collection, handling, and analysis were according to standard protocols for Australian pathology laboratories, and there were no assay variations or biases between 2005 and 2007 as judged by re-analysis of some deep-frozen samples from the first study (data not shown). Therefore, assuming the two cohorts of children concerned are generally representative of their age groups, it seems that the decline in IR between 5 and 7 yr of age may change direction somewhere between 8 and 10 yr of age, as children approach puberty or undergo adrenarche.

We also identified acceleration in the development of HOMA-IR in girls compared with the boys, and the mean HOMA-IR of the girls increased by 58% over the 2 yr compared with that of the boys increase of 30%. IR is known to increase at puberty (19), and our data were consistent with this. Of relevance is the finding that girls who were at pubic hair Tanner stage 3 at the time of the second test were measured with higher HOMA-IR values than those at Tanner stage 1 or 2. Therefore, with evidence of an advance in maturation in the girls at the time of the second round of testing, it is likely that physical maturation is an influential factor in the widening gender gap in HOMA-IR.

The lack of evidence to support the existence of the longitudinal (within-child) relationships between IR and %BF was unexpected, given the contrasting cross-sectional findings. However, our findings are consistent with those of a longitudinal study of nine healthy children measured before and during puberty (20). These workers, employing hyperinsulinemic-euglycemic and hyperglycemic clamp studies reported an absence of any relationship between insulin sensitivity and changes in %BF.

Precision of measurement has been suggested as a factor that may reduce the accuracy of calculated relationships (21), but while DXA may lack validity it does not lack reliability (22); so measurement of %BF was unlikely to have been a confounding issue in our longitudinal analyses. In any case, significant relationships between IR and %BF were observed in cross-sectional analyses. In line with the suggestion made above in relation to gender differences in HOMA-IR, the lack of evidence for longitudinal relationships between HOMA-IR and each of %BF, CRF, and PA in the girls might also be attributable to factors associated with their physical development. That we found significant longitudinal relationships between HOMA-IR with CRF and PA in the boys, where fewer numbers showed signs of advanced physical development compared with the girls, is at least consistent with this argument. It was on this premise that we recalculated the longitudinal relationships between HOMA-IR and each or %BF, PA, and CRF, confining these calculations to boys and girls still at Tanner stage 1 at the end of our study period. However, these calculations produced no variation of consequence to the longitudinal relationships reported for the groups in total. This in turn provided no support for our premise that pubertal development may have modified the nature of these relationships. On the other hand, these findings also served to indicate that pubertal development was not a confounding factor in our reported longitudinal relationships.

Our subjects were non-selected with respect to adiposity, but irrespective of limitations of body mass index (BMI) as a general surrogate of adiposity particularly in this age group (23), BMI-based classification charts (24) indicated that 24% of the boys and 26% of the girls were overweight or obese at the initial test period. With the concern that overweight children are at increased risk of developing metabolic dysfunction, clinical recommendations even in asymptomatic children are likely to include reduction of body fat. However, this general clinical consensus is based on cross-sectional studies or on clinical experiences with symptomatic children. Our longitudinal data raise questions as to the effectiveness of body fat changes in terms of controlling IR in asymptomatic 8-yr olds, as did the previously cited study involving children moving through puberty, which also failed to find any relationship between change in %BF and change in insulin sensitivity (20). Moreover, the Early Bird longitudinal study in 5 to 7-yr olds did little to support the role of changes in body fat as a mean of controlling IR at a young age, given that mean HOMA-IR of these children actually decreased as mean adiposity increased (2). It may be that changes in IR are only associated with large variations in %BF or that a longitudinal relationship between HOMA-IR and %BF only exists in children with metabolic dysfunction. We were in a position to investigate the former proposition to some extent, as the range of some individual changes in %BF were reasonably large (–4.5% to +9.3% in boys and −7.2% to +12.9% in girls). Fitting a curvilinear line to the data (not shown) revealed only very weak evidence of a relationship between change in HOMA-IR at the high ends of change in %BF, but further specific work is required to conclude one way or the other.

In the absence of evidence supporting relationships between change in %BF and HOMA-IR in asymptomatic young children, we hasten to point out that our discussion should not be interpreted as condoning overweight and obesity in children. Indeed, this would be short sighted for at least three reasons. First, significant relationships between change in %BF and change in IR may emerge as children approach adolescence. Second, obesity in childhood may predispose a variety of physical, psychological, and social problems unrelated to IR. Third, overweight and obese children tend to be less physically active.

While no evidence emerged to suggest that change in PA was related to change in IR in the girls, it was a different situation in the boys where PA was related to IR, as was CRF to a lesser degree. This contrasts with the previous longitudinal findings in 5- to 8-yr olds from Metcalf and co-workers (3) where evidence of a relationship ($p < 0.03$) between PA and HOMA-IR emerged in girls, but not in boys. This may reflect an age and physical maturity-related variation between the cohorts in the Early Bird and lifestyle of our kids (LOOK) studies. Nonetheless, our findings indicate that changes in PA, consistent with changes in %BF, are unlikely to exert any influence on IR over 2 yr in 8-yr old girls, but increasing PA may help to control the general increase in HOMA-IR in boys.

The question arises as to whether the increase in HOMA-IR we observed in the children between 8 and 10 yr of age is representative of increasing risk of metabolic dysfunction or simply a feature of normal development. There is support for the former position, especially in girls, where HOMA-IR is higher, in that there is an increasing incidence of type 2 diabetes in childhood and adolescence (25). Although this study is not designed to answer this question, one could reasonably speculate that a progressive increase in IR to defend threats to blood sugar and fat levels, to increase energy reserves, and to promote tissue growth may have evolved as part of normal physiological preparation for reproductive life.

In conclusion, we provide new longitudinal data to show that the IR of 8-yr old boys and girls increases as they move towards or enter the early stages of puberty over the next 2 yr, these increases being greater in girls. In practical terms and being careful to confine our comments to offsetting increases or reducing HOMA-IR between 8- and 10-yr olds, our longitudinal findings provide little support for any impact of changes in body fat but support for increasing PA, although the latter applies only in boys. Finally, our study, in demonstrating the conflicting outcomes of longitudinal and cross-sectional investigations of relationships, highlights the potential hazards in interpreting observational studies.

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