Age Before Stage: Insulin Resistance Rises Before the Onset of Puberty

A 9-year longitudinal study (EarlyBird 26)

Alison N. Jeffery, phd
Brad S. Metcalf, msc
Joanne Hosking, phd
Adam J. Streeter, msc
Linda D. Voss, phd
Terence J. Wilkin, md

OBJECTIVE—Insulin resistance (IR) is associated with diabetes. IR is higher during puberty in both sexes, with some studies showing the increase to be independent of changes in adiposity. Few longitudinal studies have reported on children, and it remains unclear when the rise in IR that is often attributed to puberty really begins. We sought to establish from longitudinal data its relationship to pubertal onset, and interactions with age, sex, adiposity, and IGF-1.

RESEARCH DESIGN AND METHODS—The EarlyBird Diabetes study is a longitudinal prospective cohort study of healthy children aged 5–14 years. Homeostasis model assessment (HOMA-IR), skinfolds (SSF), adiposity (percent fat, measured by dual-energy X-ray absorptiometry), serum leptin, and IGF-1 were measured annually in 235 children (134 boys). Pubertal onset was adduced from Tanner stage (TS) and from the age at which luteinizing hormone (LH) first became serially detectable (≥0.2 international units/L).

RESULTS—IR rose progressively from age 7 years, 3–4 years before TS2 was reached or LH became detectable. Rising adiposity and IGF-1 together explained 34% of the variance in IR in boys and 35% in girls (both $P < 0.001$) over the 3 years preceding pubertal onset. The contribution of IGF-1 to IR was greater in boys, despite their comparatively lower IGF-1 levels.

CONCLUSIONS—IR starts to rise in mid-childhood, some years before puberty. Its emergence relates more to the age of the child than to pubertal onset. More than 60% of the variation in IR prior to puberty was unexplained. The demography of childhood diabetes is changing, and prepubertal IR may be important.

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Amiel et al. (1) were the first to report that insulin resistance (IR) is higher in puberty. Glucose clearance was ~30% lower in children between Tanner stage (TS) 2 and TS4 compared with prepubertal children or adults. Greater fat mass (2), sex steroids (3), and higher concentrations of growth hormone/IGF-1 (4,5) have variously been proposed to explain the difference.

Several groups have replicated Amiel's observation, most reporting that IR was higher in TS2–4 than TS1 (prepuberty), and lower again by TS5 (2,4,6,7). However, of the studies making measurements at different stages of puberty (8–14), only two did so on more than two occasions in the same cohort (12,13), and then with contradictory findings. Hoffman et al. (12) found no changes in IR between TSs, once adjusted for BMI, whereas Moran et al. (13) reported a significant flux during adolescence, independent of changes in body composition. Interpretation is all the more difficult because existing longitudinal studies of IR during puberty report on groups of children of widely varying age at baseline (8–14). The youngest reported mean age was 9.2 ± 1.3 years in a repeated measures study by Goran and Gower (9). Other such studies began with children aged 9.8–13 years (8,10–13) whereas Travers et al. (14) reported only from TS2. A cohort of uniform age with measures from early childhood, in addition to measures of pubertal maturation, is needed to establish when IR begins to rise in relation to puberty.

The method used to detect pubertal onset is important for a study of pubertal IR, but the issue is not straightforward. Tanner staging classifies puberty according to anatomical responses that occur months downstream of hypothalamic activation, whereas the metabolic changes of puberty may respond to the same cues independently, and with a different tempo. Pubertal maturation of the hypothalamo-pituitary-gonadal axis reportedly begins with a rise in luteinizing hormone (LH) around 8–9 years in girls, and 1–2 years later in boys (15), although longitudinal data are few. Frisch and McArthur (16) first suggested that a critical proportion of body fat may be required for the initiation of the hypothalamo-pituitary-gonadal pubertal process, and, more recently, the adipokine leptin has been implicated as the signal responsible (17).

EarlyBird is a prospective cohort study of healthy children extending over the course of childhood, and the aims of this analysis were to establish, from longitudinal data, the trends in IR during contemporary childhood and their relationship to age, TS, LH, IGF-1, and adiposity. We were particularly concerned to establish at what age, or pubertal stage, the rise in IR started, and to what it might be attributed.

RESEARCH DESIGN AND METHODS

Participants

EarlyBird is a prospective, nonintervention cohort study that recruited 307 healthy children (170 boys) at 5 years from randomly selected schools, based in the city of Plymouth, U.K. The majority (98%) are Caucasian, with a wide socioeconomic mix representative of the U.K. as a whole (mean index of multiple deprivation score 21.7, range 6.5–73.0; U.K. mean 26.3). The protocol has been

From University Medicine, Peninsula Medical School, Plymouth, U.K.
Corresponding author: Alison N. Jeffery, alison.jeffery@pms.ac.uk.
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described in detail elsewhere (18). The main research question is, which children develop IR, and why? The cohort is of uniform age (mean age at recruitment 4.9 years, SD 0.3), children were reviewed at 12 monthly intervals (±1 month) and results are reported here from 5 to 14 years. Written consent of the parent, and assent from the child at each visit, was obtained. Ethical approval was granted in 1999. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Measures

Adiposity was measured in two ways. Skinfolds (SSF) (skinfold calipers; Holtain Ltd., Crosswell, Crymych, Dyfed, U.K.) were measured annually in duplicate by one of two trained nurses over the biceps and triceps of the left arm and subscapular, suprailiac, and para-umbilical areas, and the mean was calculated for each measure. Body fat (percent fat) was measured annually from 7 years by dual-energy X-ray absorptiometry (Lunar Prodigy Advanced fan beam system; Lunar Corporation, Madison, WI). All blood samples were taken fasting between 0900 and 0945 h and included serum insulin (DPC Immulite, Los Angeles, CA; cross-reactivity with proinsulin <1%), glucose, and LH. Glucose and LH were analyzed within 3 h of collection. Insulin was analyzed weekly in batches on serum frozen at −80°C. The interassay coefficient of variation for LH was <5.0%, and for insulin 8.0% at 2.87 mU/L. The corresponding limits of detection were <0.01 and 2.0 mU/L, respectively. Leptin and IGF-1 were measured in batches on serum stored at −85°C for 6–18 months by Naveed Sattar (University of Glasgow, Glasgow, U.K.), using an in-house radioimmunoassay validated against the commercially available Linco assay. The interassay coefficient of variation for leptin was <10% over the sample concentration range and the detection limit 0.5 ng/mL. The corresponding values for IGF-1 were <10% and 2 μg/L.

IR was derived from homeostasis model assessment (HOMA2-IR) (19). HOMA has been validated in children against the hyperinsulinemic clamp with correlations of $r > 0.9$ (20).

Pubertal measures

The EarlyBird study is concerned with metabolic more than anatomical change and, in an attempt to incorporate a more inclusive concept of puberty, its onset was defined in two ways:

1. TS self-assessment. From 9 years, each child (and their parent in the early years) was shown line drawings representing genital development for boys, breast development for girls, and pubic hair development for both, and asked to choose the picture for each that most closely matched their own development. The drawings have been validated (21) and agree, to within one TS, by 76% with clinical assessment of genital development ($\kappa = 0.48$) and 88% with pubic hair development ($\kappa = 0.68$). A mean score for both Tanner measures (genital/breast and pubic hair development) was calculated at each age. A mean score of 1.5 (e.g., genital stage 2, pubic hair stage 1) was treated as TS2, likewise a score of 2.5 was treated as TS3, etc. TS1 represents prepuberty (no phenotypic change), TS2 early puberty (first phenotypic change), TS3 mid-puberty, TS4 late puberty, and TS5 the end of puberty (adult phenotype).
2. LH. The age at which LH first became detectable at ≥0.2 units/L (and remained so subsequently) was designated LH 0. The years before LH became detectable were correspondingly designated −1, −2, etc., up to −6; and those

Table 1—*Cohort characteristics ages 5–14 years*

Age	TS1 *n* (%)	TS2 *n* (%)	TS3+ *n* (%)	LH units/L	BMIsds	% Fat	SSF (cm)	IR (HOMA)	IGF-1 (μg/L)	Leptin (ng/mL)
Boys (*n* = 134)										
5 years	—	—		0.01 (0.01)	0.19 (0.18)	—	3.63 (0.22)	0.48 (0.08)	64.72 (5.12)	2.51 (0.44)
6 years	—	—		0.01 (0.01)	0.17 (0.18)	—	3.80 (0.24)	0.36 (0.06)	82.27 (6.36)	2.53 (0.44)
7 years	—	—		0.01 (0.00)	0.21 (0.18)	2.60 (1.20)	4.17 (0.28)	0.33 (0.04)	97.51 (6.36)	2.75 (0.62)
8 years	—	—		0.01 (0.00)	0.28 (0.20)	2.66 (1.72)	4.57 (0.36)	0.37 (0.06)	106.70 (6.08)	3.19 (1.18)
9 years	107 (80)	26 (19)	1 (1)	0.03 (0.01)	0.38 (0.18)	2.78 (1.56)	5.01 (0.40)	0.52 (0.06)	138.38 (8.38)	4.53 (1.06)
10 years	104 (77)	28 (21)	2 (2)	0.15 (0.02)	0.43 (0.20)	2.90 (1.66)	5.25 (0.46)	0.76 (0.08)	137.00 (8.62)	5.31 (1.38)
11 years	91 (68)	38 (28)	5 (4)	0.58 (0.05)	0.34 (0.20)	2.96 (1.74)	5.50 (0.48)	0.69 (0.08)	131.62 (7.98)	4.06 (1.16)
12 years	19 (14)	83 (62)	32 (24)	1.14 (0.08)	0.42 (0.20)	3.03 (1.70)	5.62 (0.52)	0.83 (0.08)	151.41 (11.12)	4.76 (1.24)
13 years	9 (7)	46 (34)	79 (59)	1.84 (0.10)	0.46 (0.22)	2.97 (1.78)	5.37 (0.50)	0.86 (0.10)	—	—
14 years	0	24 (18)	110 (82)	2.50 (0.10)	0.34 (0.20)	2.90 (1.70)	5.48 (0.46)	0.90 (0.12)	—	—
Girls (*n* = 101)										
5 years	—	—		0.01 (0.00)	0.52 (0.20)	—	4.57 (0.17)	0.64 (0.08)	79.84 (6.60)	3.60 (0.80)
6 years	—	—		0.01 (0.00)	0.50 (0.20)	—	4.90 (0.21)	0.51 (0.08)	98.49 (7.28)	3.63 (1.12)
7 years	—	—		0.01 (0.00)	0.54 (0.22)	3.00 (1.72)	5.37 (0.48)	0.43 (0.06)	114.43 (8.26)	4.62 (1.32)
8 years	—	—		0.01 (0.00)	0.53 (0.22)	3.09 (2.10)	5.89 (0.50)	0.45 (0.08)	125.21 (9.02)	5.31 (1.68)
9 years	91 (90)	10 (10)	0	0.05 (0.04)	0.61 (0.22)	3.23 (1.88)	6.46 (0.58)	0.74 (0.10)	167.34 (12.50)	7.24 (1.86)
10 years	85 (84)	15 (15)	1 (1)	0.21 (0.06)	0.62 (0.24)	3.30 (1.80)	7.08 (0.60)	0.91 (0.12)	181.27 (15.84)	8.76 (2.16)
11 years	74 (74)	25 (24)	2 (2)	0.99 (0.15)	0.57 (0.24)	3.35 (1.86)	7.24 (0.60)	1.02 (0.14)	194.42 (17.72)	8.00 (1.94)
12 years	27 (27)	52 (51)	22 (22)	2.81 (0.39)	0.67 (0.24)	3.35 (1.86)	7.41 (0.62)	1.38 (0.20)	270.43 (21.46)	9.78 (1.90)
13 years	5 (5)	29 (29)	67 (66)	4.50 (0.34)	0.77 (0.26)	3.37 (1.82)	7.24 (0.68)	1.31 (0.16)	—	—
14 years	0	19 (19)	82 (81)	5.96 (0.52)	0.84 (0.24)	3.47 (1.90)	8.13 (0.60)	1.20 (0.16)	—	—

Data are means (SE) and *n* (%). BMIsds, BMI SD score.

after it became detectable were designated +1, +2, and +3. The use of a single LH measure to diagnose puberty has been described by Houk et al. (22).

Statistical analyses

Analyses were performed using SPSS version 16. Children were included in the analyses if they had HOMA-IR measures on at least 5 out of the 10 possible time points, including the 14-year measure (n = 134 boys, 101 girls). Those excluded did not differ by way of SSF, BMI SD score (BMIsds), or HOMA-IR at baseline (5 years) compared with those included (all $P > 0.21$). SSF, dual-energy X-ray absorptiometry percent fat, HOMA-IR, IGF-1, and leptin had positively skewed distributions and were log transformed for analysis.

A difference of 0.1 in the mean of HOMA-IR was deemed significant in both sexes (>80% power). With 134 boys and 101 girls, correlation coefficients above r = 0.24 (boys) and r = 0.28 (girls) would be significantly different from zero with 80% power, $P < 0.05$. Paired Student t tests compared means at different ages, and correlations were established by Pearson correlation. Linear mixed effects models provide a powerful and flexible tool for modeling longitudinal data, permitting the inclusion of repeated measures, co-correlated data, data missing at random, and inclusion of unlimited factors and covariates. Diagnostic plots of the final models showed no apparent violations of the assumptions of residual normality or homoscedasticity.

RESULTS

Cohort characteristics

The cohort characteristics from 5 to 14 years are shown in Table 1. The variance in age at each time point was small (SD, ±0.3 years), and BMI was standardized to exact age. All measures of fatness rose progressively in both sexes. Serum leptin (a marker of adiposity released exclusively by adipocytes) and IGF-1 (the hormone largely responsible for linear growth) again both rose progressively throughout.

Onset of puberty

TS. At 9 years, 19% of boys and 10% of girls self-reported TS2, and all reported TS2 by 14 years (Table 1). Boys reported TS2 (genital development) at 9.95 years, and TS2 (pubic hair development) at 11.07 years; girls at 10.66 years and 11.16 years, respectively.

Biochemical (LH). LH was undetectable in 99.8% of children from 5 to 8 years. Isolated LH values of 0.4–0.7 units/L, respectively, were detected in three individuals at 5, 6, and 8 years; all of which returned to <0.2 the subsequent year. The cumulative proportion of children with detectable LH at each age is shown in Fig. 1*A*. Although LH began to rise around the same age (9–10 years) in both sexes, its serum concentration rose more quickly in the girls (Fig. 1*B*). By 14 years, only two boys still had undetectable LH levels.

Trends in HOMA-IR

Girls had higher IR than boys at each age ($P < 0.05$). Adjusting for adiposity attenuated this sex difference, but girls remained significantly more insulin resistant at 5, 6, 13, and 14 years ($P < 0.05$). HOMA-IR fell from 5 to 7 years in both sexes, but rose thereafter, almost linearly, to 14 years (Fig. 2*A*). The trends in IR plotted during the 6 years that preceded pubertal onset (TS2) (Fig. 2*B*) and LH onset (Fig. 2*C*) illustrate clearly how IR in childhood begins to rise as many as 4 years in advance of any phenotypic or pituitary evidence of puberty in both boys and girls. A similar pattern was seen when IR was plotted in relation to onset of pubic hair (PH) development (Supplementary Fig. 1), with significant increases in IR beginning 4 years before TS2.

Models

As expected, leptin correlated strongly with SSF and percent fat (r = 0.6–0.8 in both sexes), and moderately with IR independently of percent fat (partial correlation IR and leptin; r = 0.23 [boys] and 0.32 [girls], both $P < 0.001$). In a regression analysis, change in leptin over the

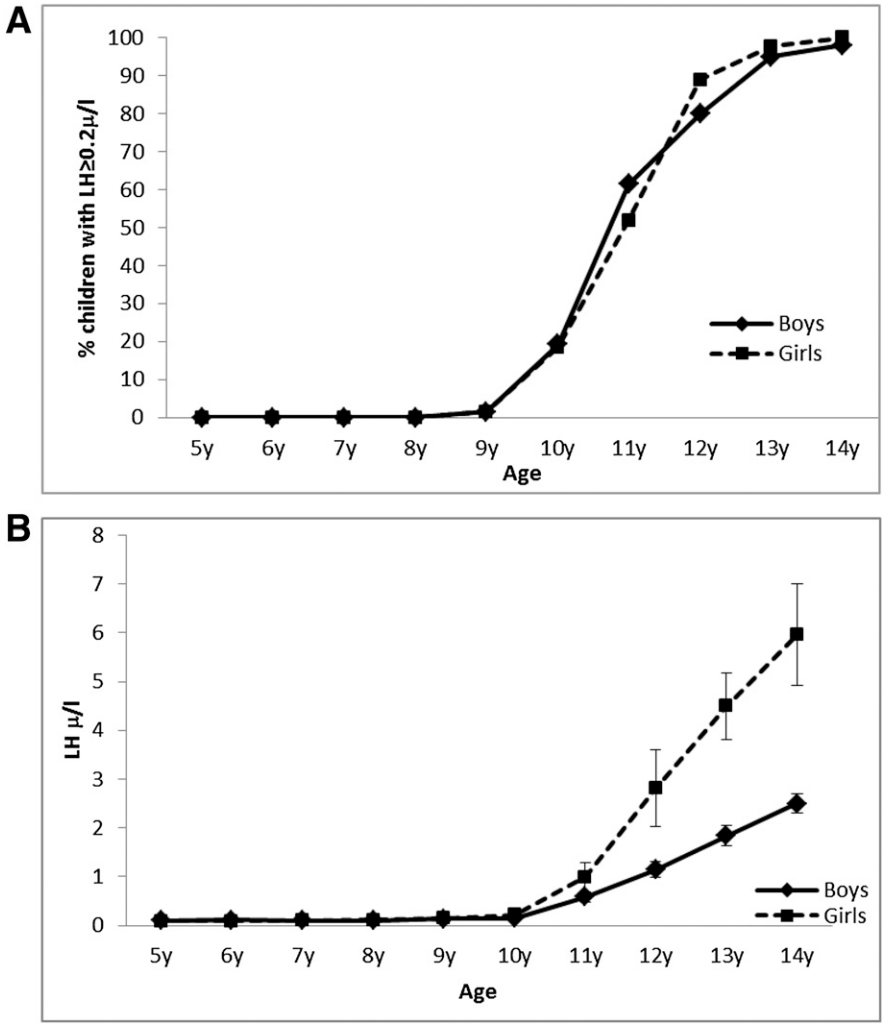

Figure 1—*LH from 5 to 14 years (y).* A*: Cumulative proportion of children with LH ≥0.2 units/L.* B*: LH mean (2 SE).*

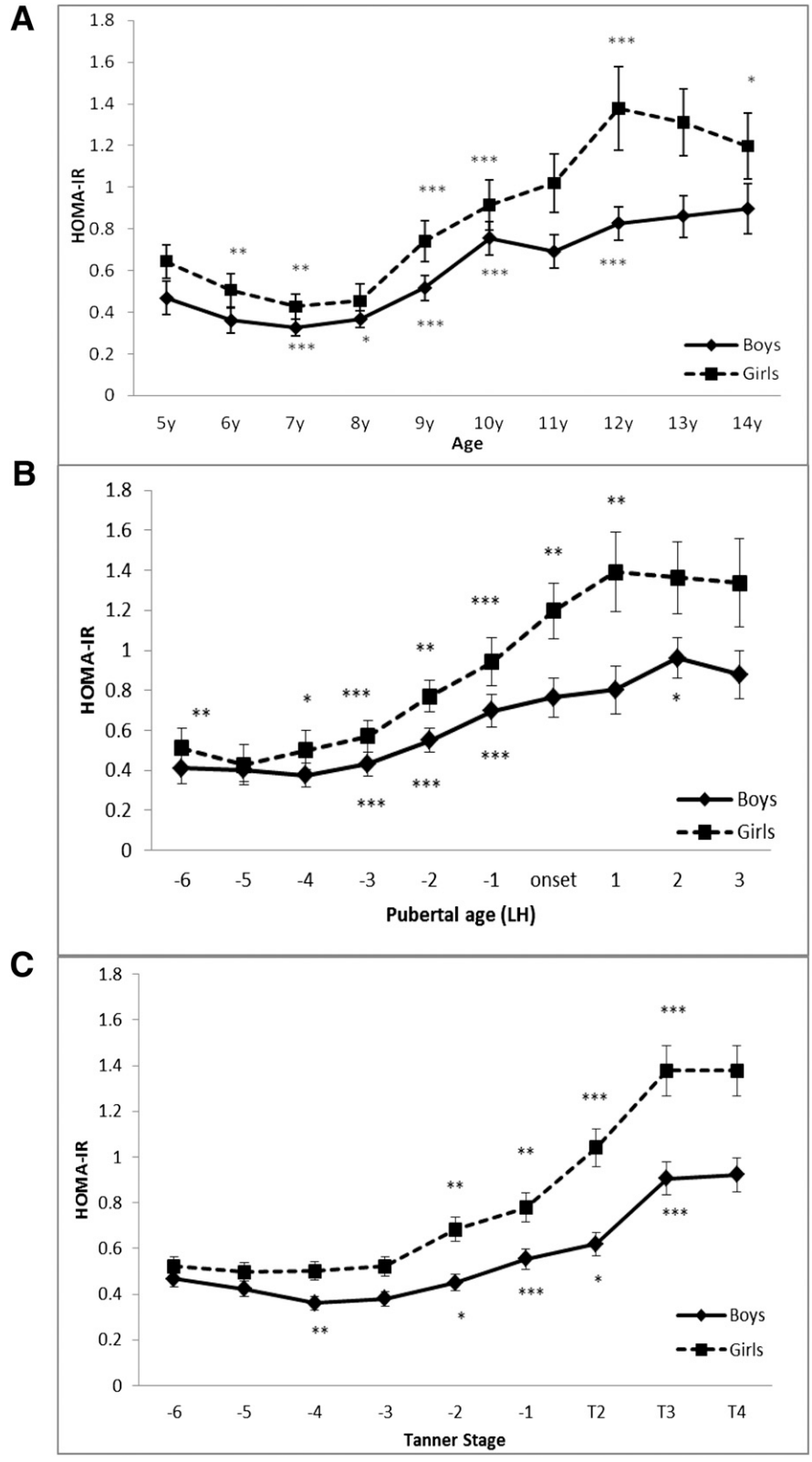

Figure 2—*HOMA-IR (mean ± 2 SE) according to chronological age* (A)*, pubertal stage by LH* (B)*, and pubertal stage by TS* (C)*. *P < 0.05; **P < 0.01; ***P < 0.001, value significantly different from preceding year (paired Student* t *test). y, year.*

3 years preceding onset of puberty (LH) was not associated with age at onset of puberty in the boys ($P = 0.8$), and was only weakly (inversely) associated in the girls ($\beta = -0.10$, $P = 0.02$). Girls with a greater increase in leptin entered puberty earlier.

The varying contributions of fat, IGF-1, and age to IR over the final four prepubertal years are shown in Table 2. Fat alone explained 25% of the variance in IR in boys (30% in girls), whereas IGF-1 contributed 17% in boys but only 6% in girls. Model 6 shows the combined effect of all three variables. Each 1% increase in fat was associated with a 2.79% (3.67%) increase in IR in boys (girls), each 1 μg/L increase in IGF-1 was associated with a 0.29% (0.21%) increase in IR, and each additional year of age was associated with 19.24% (11.29%) increases in IR.

When SSF was substituted for percent fat, the results were very similar (not shown). BMIsds alone explained 12% of the variance in IR in boys and 20% in girls (not shown).The models were repeated using data over the 4 years immediately preceding the rise in LH (LH −4, −3, −2, and −1) (Supplementary Table A1). The contributions of age, fatness, and IGF-1 were almost identical to those in Table 2 (percent fat explained 27% of the variance of IR in boys and 31% in girls; IGF-1 explained 11 and 12%, respectively; and the combination of percent fat, IGF-1, and age explained 43 and 39%, respectively).

CONCLUSIONS—The IR of early adolescence is usually attributed to puberty, but our data suggest that it emerges well before the rise in LH that initiates puberty and before any discernible physical changes. The prepubertal increase in IR was partially accounted for by increases in adiposity, with percent fat alone explaining 25 and 30% of the variation in IR in boys and girls, respectively. Type 2 diabetes is increasingly common in childhood, and the majority of diabetic children are female (23), consistent with their greater adiposity and IR. However, even when accounting for increases in percent fat, IGF-1, and age, over half of the total variance in IR remained unexplained (model 6).

We are unsure why insulin demand should begin to rise from as early as 7 years, although three observations are noteworthy. First, adiposity starts to rise around the same age, and fat is known to reduce insulin action. Second, serum IGF-1 rises progressively as puberty

Table 2—*Contributions to prepubertal IR*

Explanatory variables	Parameter estimate (95% CI), % fat	Parameter estimate (95% CI), IGF-1	Parameter estimate (95% CI), age	R^2 for model	*P* for model
Boys					
Model 1: % fat	4.18 (3.45–5.01)			0.25	<0.001
Model 2: IGF-1		0.70 (0.50–0.82)		0.17	<0.001
Model 3: age			30.47 (25.08–36.12)	0.26	<0.001
Model 4: % fat + IGF-1	3.51 (2.74–4.26)	0.48 (0.33–0.66)		0.34	<0.001
Model 5: % fat + age	3.04 (2.29–3.77)		22.75 (17.70–28.15)	0.42	<0.001
Model 6: % fat + IGF-1 + age	2.79 (2.12–3.46)	0.29 (0.16–0.42)	19.24 (14.22–24.36)	0.45	<0.001
Girls					
Model 1: % fat	4.50 (3.71–5.29)			0.30	<0.001
Model 2: IGF-1		0.40 (0.29–0.58)		0.06	<0.001
Model 3: age			22.75 (17.06–28.62)	0.19	<0.001
Model 4: % fat + IGF-1	3.97 (3.24–4.81)	0.28 (0.15–0.40)		0.35	<0.001
Model 5: % fat + age	3.87 (3.25–4.50)		13.54 (8.98–18.29)	0.36	<0.001
Model 6: % fat + IGF-1 + age	3.67 (3.05–4.39)	0.21 (0.10–0.33)	11.29 (6.61–16.18)	0.39	<0.001

Linear mixed-effects models; dependent variable log IR over last 4 years preceding TS2 (at TS −4, −3, −2, and −1). Percent fat and IGF-1 were added as fixed effects, and age was added as both a fixed and a random effect. Parameter estimates and 95% CIs are back transformed and represent the percent increase in IR for each 1 unit increase in the explanatory variable. Contribution of all individual estimates was significant at $P < 0.001$.

approaches, and the growth hormone/IGF axis is known to be associated with IR (24). In the current study, IGF-1 contributed an additional 3% to the variance of IR in both sexes, after accounting for the effects of adiposity and age. The higher IGF-1 levels in girls may relate to their greater adiposity, or may reflect the fact that low levels of estrogen produced prepubertally in girls could have a sensitizing effect on growth hormone, thereby increasing both IGF-1 and IR. Alternatively, since both insulin and IGF-1 belong to the same proinsulin superfamily, girls could be more "IGF-1 resistant" in the same way that they are more insulin resistant.

Third, adrenarche occurs around 6–8 years. Adrenarche precedes activation of the gonadal axis and is characterized by an abrupt rise in the adrenal androgen dehydroepiandrosterone (25). Although speculative, it is possible that dehydroepiandrosterone (sulfate) is responsible for the age-dependent rise in IR either directly or indirectly by promoting fat accumulation. Adrenarche has been linked before to IR in girls (3), though not in boys (26).

To our knowledge, this is the first study of puberty to track the behavior of LH alongside traditional Tanner staging. Hormonal changes inevitably precede the phenotypic changes for which they are responsible, and the sex differences in timing of Tanner staging are universally taken to mean that hormonal activation begins earlier in girls than in boys (15). Our present observations, on the other hand, suggest that puberty is signaled by LH at the same age in boys as in girls, and that it is more likely a difference in the tempo of subsequent change, than the timing of first release, that distinguishes the sexes. Whatever, IR rises well before any discernible puberty, endocrine or anatomical.

This study has strengths and weaknesses. The findings we report depended on a truly longitudinal design, annual fasting blood samples, and a cohort of uniform age to best resolve age-related changes. Together, they provided the opportunity for using multilevel modeling to detect and evaluate interactions over time (change for change analysis), a technique that is substantially more robust than simple cross-sectional association or regression. The study is nevertheless relatively small and the phenotypic changes of pubertal onset were, for ethical reasons, self-reported rather than clinician assessed. We did not record Tanner staging before the age of 9 years, but subjective overestimation almost certainly accounts for the apparently large numbers of boys entering puberty at the age of 9 years. This places constraints on the use of self-report and makes the measurement of LH an attractive (and objective) alternative marker for the timing of pubertal onset. The boys' estimation of pubic hair development appeared more plausible, however, and when IR was plotted in relation to PH rather than in conjunction with genital development, the rise in IR began 4 years before TS2 in both sexes. The use of LH as a marker of pubertal onset is novel and has yet to be widely accepted. Both LH and follicle-stimulating hormone are involved in the initiation of estrogen and testosterone production, although we report here only the behavior of LH. Finally, the observations can apply with any certainty only to children of Caucasian origin. Data collection in the EarlyBird study is still in progress and will continue to final height (adulthood).

In summary, IR is already rising from 7 years of age in contemporary boys and girls, ~3–4 years before pubertal onset, however it is defined. The rise can partly be explained by the accumulation of fat, and to a lesser extent by rising IGF-1. There remains an age-related, but unexplained, residual that might be ascribed to the rise in adrenal hormones. The demography of childhood diabetes is changing, and prepubertal IR may be important.

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A.N.J. researched data and wrote the manuscript. B.S.M., J.H., and A.J.S. assisted with data analysis and contributed to discussion. L.D.V. and T.J.W. contributed to discussion and edited the manuscript. A.N.J. is the guarantor

of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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