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Insulin Resistance and the Persistence of Obesity from Childhood into Adulthood

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Insulin resistance and obesity are associated in children as they are in adults. However, although insulin resistance seems to oppose further weight gain in adults, opposite results have been found in children. To investigate the relationship between childhood obesity, insulin resistance, and long-term weight gain, we selected 215 obese Caucasian children (120 males and 95 females) aged 10.5 (±2.4) yr, with a relative body mass index (BMI) of 153.8% (±27.7%) and normal glucose tolerance. Insulin resistance was assessed at baseline by using the homeostasis model assessment. Fourteen (±5) years later, 103 subjects returned for a follow-up examination of height and weight. At follow-up, 37 subjects (36%) were obese (BMI ≥ 30), 33 (32%) were overweight (25 ≤ BMI < 30), and 33 (32%) were of normal weight (20 ≤ BMI < 25). In a multiple regression, relative BMI and insulin resistance at childhood were independent predictors of adulthood BMI ($r^2 = 0.44$; $P < 0.01$) in girls. A multivariate logistic regression analysis showed that high relative BMI [odds ratio, 1.06; 95% confidence interval, 1.00–1.13; $P = 0.04$] and low insulin resistance index at baseline (odds ratio, 0.58; 95% confidence interval, 0.34–0.99; $P = 0.04$) predicted obesity in adulthood for girls, no matter their age, Tanner stage, and their parents' BMI. In boys, insulin resistance was not a significant predictor of adult obesity.

In conclusion, obesity tracks into adulthood for many obese Caucasian children. In obese girls, insulin resistance during childhood appears to oppose the risk of obesity in adulthood. (*J Clin Endocrinol Metab* 87: 71–76, 2002)

CHILDHOOD OBESITY IS a risk factor for adult morbidity and mortality, independent of BMI in adulthood, familial history of cardiovascular diseases or cancer, and smoking (1). Moreover, obese children run a high risk (~50%) of also being obese as adults (2). The persistence of obesity from childhood into adulthood also may favor an early onset of diabetes, as suggested by the recent trend of the early onset of type 2 diabetes in individuals who have suffered from obesity since childhood (3).

Several factors may potentially affect the tracking of obesity across ages; insulin resistance has been suggested as one of these factors. However, although a relationship between insulin resistance and fat gain has been demonstrated, it is not clear whether insulin resistance is a promoting factor or simply a consequence of fat gain (4). Regarding this aspect, there are contrasting data for adults and children. Two longitudinal studies conducted on Pima Indian adults showed a protective effect of insulin resistance against further weight gain (5, 6). Consistent findings have resulted from other longitudinal studies on different adult populations: Caucasians, Mexican Americans, Creoles, Chinese, and Asian Indians (7–11). However, contrasting data were found in children; in Pima Indians, high fasting insulin levels for children between the ages of 5 and 9 yr were associated with a greater weight gain during a 9-yr follow-up study (12). Consistent results were recently reported for a sample of Caucasian and African-American children, studied at a mean age of 8.1 (±1.6) yr and followed over 3–6 yr (13). As a whole, these findings suggest that hyperinsulinemia and insulin resistance may favor fat gain during childhood and adolescence, whereas they oppose fat gain in adulthood.

To our knowledge, no studies have assessed the relationship between insulin resistance during childhood and obesity during adulthood. The aim of the present study was to investigate the relationship between childhood obesity, insulin resistance, and long-term weight gain in Caucasian children, followed into adulthood.

Abbreviations: BMI, Body mass index; CI, confidence interval; HOMA, homeostasis model assessment; IR_{HOMA}, insulin resistance index; OR, odds ratio; relBMI, relative BMI.

Materials and Methods

Subjects and experimental protocol

Two hundred fifteen Caucasian children (120 males and 95 females), aged 10.5 (±2.4) yr, were recruited from among the overweight children who attended the outpatient clinic of the Department of Pediatrics at the University Hospital in Verona, Italy. Each child underwent a complete physical examination, including anthropometric measures. Puberty development was clinically assessed on the basis of Tanner stages (14). Height and weight were measured in postabsorptive conditions and with an empty bladder. Height was measured to the nearest 0.5 cm on a standard height board, and weight was determined to the nearest 0.1 kg on a standard physician's beam scale with the subject dressed only in light underwear and no shoes. The body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Children with a BMI greater than the 95th percentile of BMI for age and sex reported on the BMI tables of Must *et al.* (15) were defined as obese. Children with a BMI between the 85th and 95th percentile were defined as overweight. To express the weight excess as a continuous variable, obesity was also defined as relative BMI (relBMI) greater than 120%, where relBMI = (BMI/BMI at the 50th percentile for age and gender) × 100. The relBMI of the children was calculated again using the BMI percentiles of Must *et al.* (15) as a reference. The parents' self-reported height and weight were used to calculate their BMI (16). Complete data were obtained from all of the children and their parents at baseline.

All of the children were given an oral glucose tolerance test. After a 12-h overnight fast, the subjects ingested a solution containing 45 g/m^2 dextrose, and venous blood samples were obtained at 0, 30, 60, and 120 min to measure plasma glucose and insulin levels. According to current criteria (17), all of the children had normal glucose tolerance.

Insulin resistance was assessed at baseline by using the homeostasis model assessment (HOMA) (18), a method applicable to epidemiological studies. HOMA allows the examiner to estimate insulin resistance using plasma insulin and glucose. The insulin resistance index (IR_{HOMA}) was calculated as follows: Ins_0 (pmol/liter) × $Gluc_0$ (mmol/liter)/135, where Ins_0 was the plasma insulin concentration and $Gluc_0$ was the plasma glucose concentration before glucose ingestion. This parameter was closely related to more accurate measurements of insulin sensitivity, such as those obtained with the glucose clamp technique in adults with various degrees of insulin sensitivity and glucose tolerance, including type 2 diabetes (19). HOMA has not been directly validated in children; however, circulating insulin levels, which are the main determinants in obtaining the HOMA score in euglycemic subjects, are a reliable index of insulin resistance also in children, as demonstrated by the close relationship with measure values obtained with the glucose clamp (20).

Fourteen (±5) years later, the subjects were invited to come back to the university's pediatric clinic for a follow-up examination, and 103 of them agreed to participate in the follow-up study. Of the 112 subjects who did not participate in the follow-up, we were not able to contact 61 of them because of a change in address and telephone number; 51 who were contacted declined to take part. Gender distribution ($\chi^2 = 5.79$; P = NS), anthopometric variables, and hematochemical parameters at baseline of the children who did not participate in the follow-up were not significantly different from those who did (Table 1).

In the follow-up examination, height and weight were measured as described above. Adults with a BMI greater than 30 kg/m^2 were defined as obese (21). Informed consent was obtained from each individual, and our protocol was performed according to the 1975 Helsinki Declaration and 1983 revision.

Biochemical analysis

Plasma glucose concentrations were measured using a glucose oxidase method. Serum insulin concentrations were determined by a specific RIA (cross-reactivity with human proinsulin <5%), using a Biosource Technologies, Inc. kit (Fleurus, Belgium). Sensitivity was 1 μU/ml, and the intra-assay coefficient of variation was 4.0%.

Statistical analysis

Baseline variables are described as the medians and ranges of the groups. Differences between genders were analyzed using the *t* test for unpaired samples or the Mann-Whitney *U* test when indicated. A zero-order correlation was performed to assess unadjusted association between insulin resistance (IR_{HOMA}), obesity (relBMI), and parents' BMI at baseline. To satisfy assumptions of normality, IR_{HOMA} was log-transformed, and BMI at follow-up required reciprocal transformation. Because of differences in insulin resistance between males and females around the age of puberty, multiple regression analyses were performed separately in the two sexes to assess the effect of baseline variables (parents' BMI, relBMI, IR_{HOMA}, age at recruitment, puberty status) and years of follow-up on body size (reciprocal BMI) in adulthood.

Finally, the subjects were divided into the following groups on the basis of their BMI in adulthood: group A, BMI less than 30 kg/m^2; group B, BMI at least 30 kg/m^2. To find out just how predictable insulin resistance, age, Tanner stage, relBMI, and parents' BMI at baseline were for the possibility of being obese as an adult, we performed multivariate logistic regression analyses for each gender, with an evaluation of the model using three goodness-of-fit χ^2 statistics. These analyses were also run using insulin, or its log when indicated, instead of IR_{HOMA}.

In all of the analyses, a probability level of P less than 0.05 was used to indicate statistical significance. All statistical analyses were performed using the SPSS v. 9.0 software for Windows package for personal computers (SPSS, Inc., Chicago, IL).

TABLE 1. Physical characteristics and biochemical parameters of children at baseline

	Children participating in the follow-up		Children refusing the follow-up		Children lost at the follow-up	
	Males (n = 66)	Females (n = 37)	Males (n = 28)	Females (n = 27)	Males (n = 26)	Females (n = 31)
Age (yr)	10.9 (4.8–15)	9.5 (5.4–15.2)	9.8 (4.6–14.7)	10 (5.1–16)	10.4 (4.5–13.5)	10 (5–14.6)
Weight (kg)	55.4 (33.5–95.5)	50.2 (26–72.5)[a]	52.2 (21–96)	53.7 (16.4–90)	55.5 (32.5–84.7)	51.5 (33–85.3)
Height (cm)	145 (110–181)	139.7 (118–159)	139 (92–167)	139 (82–172.5)	146 (126–170)	142 (112–165)
BMI (kg/m^2)	25.5 (17.8–45.4)	25.1 (18.7–32.5)	26.8 (20.2–41)	26.6 (21.6–38)	25.8 (20.4–34.4)	25.4 (17.1–35)
relBMI (%)	149 (105–226)	148 (114–199)	158 (110–215)	155 (118–201)	150 (115–195)	148 (108–184)
Father's BMI (kg/m^2)	26.6 (20.9–44.1)	26 (21.6–34.6)	27 (21.1–34)	26.9 (22–32.4)	26.4 (20.8–35.2)	25.9 (21–34.3)
Mother's BMI (kg/m^2)	24.4 (15.1–34.6)	24 (18.4–37.8)	25 (18.9–32)	24.6 (18.5–38)	24 (19–31.4)	24.2 (17.6–31.5)
Fasting glucose (mmol/liter)	5.3 (3.3–6.2)	5.1 (2.9–7)	5.1 (3.6–5.8)	5.1 (4–5.9)	4.9 (4.5–5.5)	4.8 (2.9–6)
2-h plasma glucose (mmol/liter)	5.8 (2.9–7.9)	6.1 (3.5–8.6)	6 (2.8–8)	5.9 (3–8.5)	5.8 (2.7–8.2)	5.7 (3.1–7.8)
Fasting insulin (pmol/liter)	93.3 (50.2–200.9)	82.5 (28.7–251.1)	96.8 (35.9–165)	98.8 (57.4–222.8)	100.6 (57.4–228.3)	105.3 (50.2–300.6)
2-h plasma insulin (pmol/liter)	229.6 (35.9–975.8)	215.3 (14.4–1,765)	230.2 (40–1,125)	224.8 (38.4–987.2)	220.1 (25.8–1,096)	216.3 (18.1–1,512)
IR_{HOMA}	3.4 (1.4–7.9)	2.9 (0.9–8.4)	3.4 (0.9–6.6)	3.9 (1.7–10.1)	3.7 (1.9–10.5)	3.8 (0.7–10.8)

IR_{HOMA}, Insulin resistance estimate, as obtained by the homeostasis model assessment.
Data are shown as median (range). No differences were found between subjects participating and not participating in the follow-up.
[a] $P = 0.02$ *vs.* males.

Results

Baseline physical and metabolic characteristics of subjects

The physical and metabolic characteristics at baseline of the children who participated in the follow-up are shown in Table 1, which also shows the same characteristics for the children who declined to participate in the follow-up and those lost at follow-up. All groups showed similar characteristics.

Of the children participating in the follow-up, 65 (63% of the total, 59% of females, and 66% of males) were at the prepuberty age (Tanner stage 1); 20 children (19% of the total, 19% of females, and 19% of males) were at Tanner stage 2; 11 children (11% of the total, 13% of females, and 9% of males) were at Tanner stage 3; and 7 (7% of the total, 9% of females, and 6% of males) were at Tanner stage 4. At baseline, no significant differences were found between males and females for each of the parameters examined, except for weight. The children showed a wide range of weight excess: 77% of them were obese (BMI > 95th percentile of BMI of reference tables), and 23% were overweight (85th < BMI < 95th percentile). Univariate analysis showed no significant correlation between relBMI and age at recruitment, $(\log_{10})IR_{HOMA}$, and parents' BMI. The mean value of the IR_{HOMA} for all children was 3.84 (0.99–8.69). IR_{HOMA} was not significantly different in the females and males in both prepuberty-aged [3.27 (±2.1) *vs.* 3.84 (±1.6), respectively; $P = 0.26$] and puberty-aged groups [4.49 (±2.4) *vs.* 3.92 (±1.3), respectively; $P = 0.36$]. Neither were any significant differences found in IR_{HOMA} between prepuberty- and puberty-aged male or female children.

Follow-up examination

After a mean follow-up of 14 (±5) yr, the subjects were on average overweight (BMI, 29 kg/m^2) (Table 2); 37 were obese (BMI ≥ 30), 33 were overweight (25 ≤ BMI < 30), and 33 were of normal weight (20 ≤ BMI < 25). No significant differences were found between males and females regarding the parameters examined, except for height. Of the 79 subjects (53 males and 26 females) who were obese in childhood, 34 (20 males and 14 females) remained obese as adults, 23 (17 males and 6 females) were still overweight but not obese (25 ≤ BMI < 30), and 22 (15 males and 7 females) became of normal weight. Of the 24 (14 males and 10 females) children who were overweight at recruitment, 10 (6 males and 4 females) remained overweight as adults, 3 (1 male and 2 females) became obese, and 11 (7 males and 4 females) became of normal weight.

TABLE 2. Physical characteristics and biochemical parameters of subjects at follow-up

	Males (n = 66)	Females (n = 37)
Age (yr)	25 (14–33.3)	25.8 (14.9–35.4)
Weight (kg)	82.7 (47–148)	78.4 (55–133)
Height (cm)	173 (157–198)	166.5 (154–185)[a]
BMI (kg/m^2)	27.1 (18.4–48.3)	27.4 (17.8–45.8)

Data are shown as median (range).
[a] $P < 0.001$ *vs.* males.

The correlation between baseline values and BMI in adulthood

BMI of adult, expressed as its reciprocal, correlated negatively with relBMI at baseline ($r^2 = -0.27$; $P < 0.01$) (Fig. 1). No significant correlation was found between BMI of adult, age at recruitment, duration of follow-up, and parents' BMI.

In females, multiple regression analysis showed that childhood overweight (relBMI), adjusted for age, puberty, and parents' BMI, was the most important predictor of BMI in adulthood ($r^2 = 0.23$; $P < 0.01$). Insulin resistance ($\log_{(10)} IR_{HOMA}$) had a significant additional effect on the prediction of obesity in adulthood ($r^2 = 0.21$; $P = 0.02$). Increased BMI in adulthood was thus predicted by a high relBMI at baseline, whereas insulin resistance at childhood played a protective role, reducing the risk of becoming obese as an adult. The entire model had an $r^2 = 0.44$ ($P < 0.01$) (Table 3). A multivariate logistic regression analysis was performed to assess baseline predictors of obesity (BMI ≥ 30 kg/m^2) in adulthood. Again, relBMI at baseline [odds ratio (OR), 1.06; 95% confidence interval (CI), 1.00–1.13; $P = 0.04$] and insulin resistance (OR, 0.58; 95% CI, 0.34–0.99; $P = 0.04$) independently contributed to predicting obesity in adulthood (Table 4). Thus, in this group of obese Caucasian females, obesity was associated with a higher relBMI in childhood and a lower insulin resistance at baseline. Age at recruitment, Tanner stage, and parents' BMI did not significantly affect BMI in adulthood.

In males, multiple regression analysis showed that the age of the boys at recruitment, adjusted for the level of overweight (relBMI), puberty, and parents' BMI, was the only significant predictor of BMI in adulthood ($r^2 = 0.21$; $P < 0.01$). Insulin resistance ($\log_{(10)} IR_{HOMA}$) did not show a significant additional effect on the prediction of obesity in adulthood (Table 3). A multivariate logistic regression analysis, performed to assess baseline predictors of obesity (BMI ≥ 30 kg/m^2) in adulthood, showed that, in this group of obese boys, age at recruitment, Tanner stage, level of overweight, parents' BMI, and insulin resistance did not have a significant predictive effect.

Similar results were obtained when fasting insulin (or its log, when indicated) were used instead of IR_{HOMA} in the analyses. In particular, multiple regression analysis showed

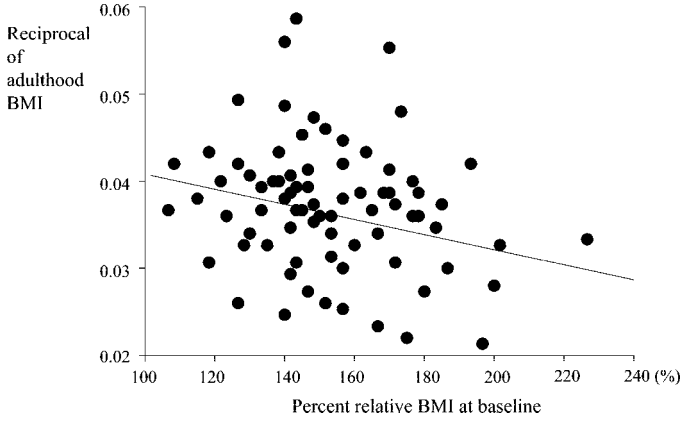

FIG. 1. Relationship between reciprocal of BMI at adulthood and the percentage of relative BMI at baseline.

TABLE 3. Multiple regression analysis in the total sample: final model

	R^2	Coefficient	SE	*P*
Females				
Dependent variable: reciprocal of adult's BMI	0.44			
Independent variables				
relBMI (%)		−1.57 E-04	0.000	0.02
Age (years)		−2.22 E-05	0.001	NS
$\log_{10}$ IR_{HOMA}		1.35 E-02	0.004	0.006
Father's BMI (kg/m^2)		−7.12 E-04	0.000	NS
Mother's BMI (kg/m^2)		3.93 E-05	0.000	NS
Puberty: 0 = prepubertal 1 = pubertal		−4.06 E-03	0.003	NS
Constant		7.33 E-02	0.02	<0.001
Males				
Dependent variable: reciprocal of adult's BMI	0.21			
Independent variables				
relBMI (%)		−7.12 E-05	0.000	NS
Age (years)		−1.19 E-03	0.001	0.02
$\log_{10}$ IR_{HOMA}		3.59 E-03	0.005	NS
Father's BMI (kg/m^2)		−2.53 E-04	0.000	NS
Mother's BMI (kg/m^2)		−2.43 E-04	0.000	NS
Puberty: 0 = prepubertal 1 = pubertal		4.38 E-03	0.002	NS
Constant		6.99 E-02	0.01	<0.001

The reciprocal of adult's BMI was used as the dependent variable. Age, pubertal status, parents' BMI, $\log_{10}$ IR_{HOMA}, and relBMI were used as independent variables.

TABLE 4. Multivariate logistic regression analysis

	OR	95% CI	*P*
Females			
Independent variables			
relBMI (%)	1.06	1.00–1.13	0.04
IR_{HOMA}	0.58	0.34–0.99	0.04
Age (yr)	0.96	0.50–1.83	NS
Pubertal status	3.92	0.25–61.16	NS
Father's BMI (kg/m^2)	1.43	0.92–2.23	NS
Mother's BMI (kg/m^2)	0.88	0.65–1.19	NS
Males			
Independent variables			
relBMI (%)	1.02	0.99–1.05	NS
IR_{HOMA}	1.03	0.67–1.58	NS
Age (yr)	1.28	0.88–1.85	NS
Pubertal status	0.27	0.05–1.50	NS
Father's BMI (kg/m^2)	1.19	0.98–1.44	NS
Mother's BMI (kg/m^2)	1.18	0.98–1.43	NS

BMI at follow-up was used as a grouping variable (group A, BMI < 30 kg/m^2; group B, BMI ≥ 30 kg/m^2), and age, pubertal status, parents' BMI, IR_{HOMA}, and relBMI were used as independent variables.

that the girls' overweight (relBMI) adjusted for age, puberty, and parents' BMI was the most important predictor of BMI in adulthood ($r^2 = 0.23$; $P < 0.02$). Fasting insulin resistance ($\log_{10}$) had a significant additional effect on the prediction of obesity in adulthood ($r^2 = 0.21$; $P = 0.05$). The entire model had an $r^2 = 0.44$ ($P < 0.02$). The multivariate logistic regression analysis similarly showed that relBMI at baseline (OR, 1.07; 95% CI, 1.00–1.13; $P = 0.03$) and fasting insulin (OR, 0.98; 95% CI, 0.96–0.99; $P = 0.04$) independently contributed to predicting obesity in adult women.

Also in males, the use of plasma insulin in place of IR_{HOMA} did not change the results of the multiple regression analysis (data not shown).

Discussion

In this population of Caucasian children, approximately 43% of the children who were obese in childhood were still obese as adults; of the remaining subjects, 29% were overweight (25 ≤ BMI < 30) as adults, and only 28% became of normal weight. In females but not in males, the severity of obesity in childhood increased the likelihood of their still being overweight as adults. The obvious clinical implication of the persistence of obesity from childhood to adulthood is the prolonged adverse effect of established cardiovascular risk factors associated with body fatness, such as an unfavorable lipid profile, hypertension, increased circulating insulin levels, and altered glucose tolerance (22–24), which cluster with obesity even at a young age (25). It has been reported that the rate of weight and body mass increase during the first two decades of life predicts the increase in serum insulin levels and the extent of alterations of several cardiovascular risk factors (26). Moreover, the duration of obesity has been considered an independent predictor of type 2 diabetes (3). Thus, it is not surprising that the persistence of obesity from childhood into adulthood is associated with increased adult morbidity and mortality and that it is more frequent than predicting factors suggest, depending on how overweight one is as an adult (1).

However, the most interesting finding of this study was that the extent of insulin resistance (IR_{HOMA}) in overweight girls, but not in boys, was an independent protective factor of obesity in adulthood. In this study, the impact of insulin resistance in childhood on predicting obesity in women was quite relevant: the increase of one unit (~27% of baseline mean value) of IR_{HOMA} in an obese girl decreases her risk of being obese as an adult by 42%. Similar results were obtained when fasting insulin was used instead of IR_{HOMA}. This finding was not affected by the level of overweight at childhood, age, puberty stage, and parents' BMI. Moreover, another statistical approach, such as a multivariate logistic regression analysis, consistently showed that, adjusted for age, puberty status, relative BMI, and parents' BMI, insulin resistance

(IR_{HOMA}) was a significant protective factor against obesity in women.

The inverse relationship between insulin resistance during childhood in girls and their BMI in adulthood is consistent with previous longitudinal studies conducted on adults (5, 6). In nondiabetic Pima Indians, insulin resistance, assessed by the euglycemic hyperinsulinemic clamp technique, was associated with a lower body weight gain in a 3.5-yr follow-up study (5). Similarly, another study on nondiabetic Mauritians (including Asian Indian, Creole, and Chinese subjects) showed that over a 5-yr follow-up period, insulin resistance was negatively associated with weight gain (9). Data from the San Antonio Heart Study on Mexican Americans and non-Hispanic whites consistently identified hyperinsulinemia as an independent predictor of weight loss after an 8-yr follow-up in the subgroup of obese nondiabetic participants (8). Finally, similar results were found for Hispanics and non-Hispanic whites by Hoag *et al.* (11). As a whole, these findings support the hypothesis that insulin resistance is mainly a consequence of obesity and that it may be an adaptive mechanism that opposes further fat gain in adults.

Few data are available on the relationship between obesity and insulin resistance in children. Odeleye *et al.* (12) studied the association of fasting plasma insulin with weight gain in overweight (average relative weight 119 ± 24%; range, 79–215%) Pima Indian children, with a 9-yr follow-up study period. The rate of weight gain per year for these children was directly associated with fasting insulin levels, adjusted for age, sex, initial relative weight, and change in height, which suggests that, contrary to what has been reported on adults, insulin resistance in young children is a risk factor for the development of obesity. Similar results were recently obtained by Johnson *et al.* (13) in a sample of 137 mostly nonobese Caucasian and African-American children of both sexes with a mean age at baseline of 8.1 yr. These authors reported that fasting insulin was positively associated with the rate of increase in fat mass during 3–6 yr. Moreover, in 71 of these subjects, who had insulin sensitivity estimated by the tolbutamide-modified iv glucose tolerance test, this measurement was negatively associated with an increase in fat mass (13). Conversely, our data for Caucasian girls are consistent with results obtained for adults.

The different results obtained in these studies are not easily explained. Differences in the methods used to assess insulin resistance seem an unlikely explanation. Most studies estimated insulin resistance by fasting insulin levels, which did not prove to be highly correlated with more accurate methods for measuring insulin resistance (27). However, in our study, the results obtained using IR_{HOMA} were comparable to those obtained using fasting insulin levels. Moreover, Johnson *et al.* (13) reached similar conclusions by using fasting insulin levels or the iv glucose tolerance test-derived insulin sensitivity index.

Another factor may be the different design of these children's studies. In the Odeleye *et al.* (12) and Johnson *et al.* (13) studies, the effects of childhood obesity and insulin resistance were measured as weight change per year during adolescence. On the other hand, in our study the comprehensive effects of childhood obesity and insulin resistance were measured as BMI at adulthood. Therefore, the two previous designs evaluated different aspects of the relationship between childhood obesity and obesity in later life.

The Pima Indians living in Arizona have a high-fat diet, which is less common in Italian children (28, 29). A fat-rich diet is expected to enhance the peripheral effects of insulin, which plays a central role in modulating nutrient disposal in the peripheral tissues where insulin drives preferential oxidation from carbohydrates over fat and promotes fat storage. Thus, one could speculate that the differences in dietary fat may, at least in part, explain the differences in insulin effects on weight changes during growth. However, it is not possible to evaluate potential dietary differences between our subjects and those living in Alabama, who were recruited in the Johnson *et al.* (13) study.

In adults, a negative feedback relationship has been consistently demonstrated between weight gain and insulin resistance, where an increase in weight promotes a progressive increase in insulin resistance, slowing down the rate of further weight gain in the subject (5). On the basis of these findings, it appears that a certain degree of insulin resistance must be reached in overweight individuals to oppose further weight gain.

Interestingly, in previous studies in adults, the negative relationship between fasting insulin and fat mass increase was stronger in more obese subjects (5). Therefore, it may also be a threshold level in this phenomenon. From this point of view, it may be observed that our children were more obese than those studied by either Odeleye *et al.* (12) or Johnson *et al.* (13). Our study represents the first prospective assessment of the relationship between insulin sensitivity and obesity throughout the entire period from childhood to adulthood. These data support the conclusions of previous studies in adults suggesting that, at least in females, insulin resistance may play a protective role in fat mass gain. As a whole, previous data for children and adults as well as our results support the hypothesis that the relationship between insulin resistance and fat mass gain may be a dynamic phenomenon that alters with age. In the first phase, during childhood, muscle insulin resistance may favor fat accumulation by impairing glucose use in this tissue, whereas the associated compensatory hyperinsulinemia may stimulate fat deposition in insulin-sensitive adipose tissue. In a second phase, in adulthood, impaired insulin action also in the adipose tissue may oppose further fat accumulation.

The reasons why insulin resistance may be a protective factor against obesity in later ages in female, but not male, obese children are not known. It may be speculated that at puberty the higher insulin resistance of girls may reflect their higher fat mass to skeletal muscle mass ratio. First, during puberty fat mass increases much more in girls than in boys, both in absolute value (kilograms) and in relative value (percentage body weight) (30). Second, during puberty girls have physiologically higher levels of insulin resistance than boys (31). Consistently, a recent study using the euglycemic clamp technique showed that insulin resistance during puberty was higher in females than in males, and this was partially explained by a difference in adiposity (32). Third, fatness and insulin resistance are associated (33, 34). In the present longitudinal study, due to the unavailability of accurate meth-

ods for assessing adiposity at the time of recruitment (1980s), BMI was used as an index of adiposity. A good level of correlation between BMI and the percentage of body fat measured by dual energy x-ray absorptiometry was demonstrated in both boys and girls (35), although the accuracy of BMI in predicting fatness was poor in any individual child (35). Therefore, by design, it might not be possible to evaluate the absolute effect of adiposity *per se*.

In conclusion, the results of this study showed that many obese Caucasian children are still obese as adults. The tracking of obesity is predicted by childhood obesity. In the obese girls, but not in the boys, insulin resistance seemed to reduce the risk of obesity in adulthood.

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