Why are nutritionally stunted children at increased risk of obesity? Studies of metabolic rate and fat oxidation in shantytown children from São Paulo, Brazil

Daniel J Hoffman, Ana L Sawaya, Ieda Verreschi, Katherine L Tucker, and Susan B Roberts

ABSTRACT
Background: Previous research suggested that nutritionally stunted children may have increased risk of obesity, but little is known about potential underlying mechanisms.
Objective: We sought to test the hypothesis that stunted children have a low metabolic rate and impaired fat oxidation relative to nonstunted children.
Design: The subjects were 58 prepubertal boys and girls aged 8–11 y from the shantytowns of São Paulo, Brazil. Twenty-eight were stunted (height-for-age z score < −1.5) and 30 had similar weight-for-height but normal height (height-for-age z score > −1.5). Parents of children in the 2 groups had equivalent height and body mass index values. Fasting and postprandial energy expenditure, respiratory quotient (RQ), and substrate oxidation were measured with indirect calorimetry in a 3-d resident study in which all food was provided and body composition was measured with dual-energy X-ray absorptiometry.
Results: Stunted children had normal resting energy expenditure relative to body composition compared with control children (4559 ± 90 and 4755 ± 86 kJ/d, respectively; $P = 0.14$) and had normal postprandial thermogenesis (2.4 ± 0.3% and 2.0 ± 0.3% of meal load, respectively; $P = 0.42$). However, fasting RQ was significantly higher in the stunted group (0.92 ± 0.009 compared with 0.89 ± 0.007; $P = 0.04$) and consequently, fasting fat oxidation was significantly lower (25 ± 2% compared with 34 ± 2% of energy expenditure; $P = 0.01$).
Conclusions: Childhood nutritional stunting is associated with impaired fat oxidation, a factor that predicted obesity in other at-risk populations. This finding may help explain recent increases in body fatness and the prevalence of obesity among stunted adults and adolescents in developing countries.

KEY WORDS
Fat oxidation, obesity, stunting, energy expenditure, children, metabolic rate, respiratory quotient, malnutrition, undernutrition, Brazil

INTRODUCTION
The prevalence of obesity is increasing worldwide, even in developing countries that have traditionally experienced high rates of undernutrition (1, 2). Countries in economic transition from undeveloped to developed, such as China, Brazil, and South Africa, are particularly affected and have an increasing prevalence of obesity across all economic levels and age groups (3). Traditional explanations for these observations include reduced physical activity and consumption of high-fat diets. However, there is still no consensus about the importance of these factors, even for individuals in developed countries (4–9).

Research has suggested that undernutrition in early life may play a role in promoting adult obesity. In particular, studies on 3 continents showed that nutritional stunting, which is usually caused by chronic undernutrition (10), is positively associated with adult fatness (11–14). In addition, we previously observed an association between excess weight gain and dietary fat content in stunted Brazilian children but not in nonstunted control children (14). This is suggestive of an increase in the efficiency of dietary fat utilization that could lead to increased body fat content over time. Consistent with these observations, permanent effects of early diet on long-term energy regulation have been observed in both rodents and nonhuman primates (15–21). However, researchers still need to identify the underlying mechanisms by which early nutritional stunting may lead to an increased risk of obesity, both to provide a rational basis for understanding the observed effects and to rule out the possibility that unrecognized confounding factors influenced the results obtained.

The general concept that early-life stimuli may have permanent effects on metabolism and development was first shown conclusively by Hubel and Wiesel (22), who observed a critical period in the early development of cats during which deprivation of visual stimuli resulted in permanent loss of sight. The concept of critical periods is consistent with the literature on childhood nutrition, which shows a generalized programming effect of early diet on metabolism, growth, and cognition (23–25). The mechanisms
by which early nutrition exerts long-term programming effects in humans are not known, but proposed mechanisms include functional alterations in growth processes, gene expression, cell number, and clonal selection within organs and tissues (24, 26, 27).

The purpose of this study was to test the hypothesis that nutritional stunting is associated with impaired fat oxidation, a factor previously shown to strongly predict body fat gain in other populations at risk of obesity, including Pima Indians (28), weight-reduced obese women (29–31), and middle-aged men (32). We also examined the possibility that stunted children might have low resting metabolic rate, a factor that predicted subsequent body fat gain in some (33–35), but not all (36, 37), prospective studies of high-risk populations.

SUBJECTS AND METHODS

Subjects

Children were identified as potential subjects during population surveys of 3 shantytowns in the city of São Paulo, Brazil. More than 300 children aged 7–11 y were weighed and measured and were found to be potentially eligible to participate on the basis of anthropometric criteria. All subjects had to have a normal weight-for-height z score (WHZ of −2.0 to 1.5) according to the National Center for Health Statistics (NCHS) standards (38). Children recruited for the control group (n = 28) had to have a height-for-age z score (HAZ) < −1.5, and children recruited for the control group (n = 30) had to have an HAZ > −1.5. Note that well-nourished Brazilian children grow adequately relative to NCHS standards in terms of both weight and height (39) and that low HAZ is widely believed to be a result of chronic, moderate undernutrition (10). In addition, the 2 groups were matched for age and WHZ. The characteristics of the study children and their parents are shown in Table 1. Although it was not possible to match stunted and control children for parental height and weight, these values were measured in all families in which the biological parents lived with the children; there were no significant differences between the groups (Table 1).

Subjects who appeared to be eligible for the study on the basis of weight and height and who were willing to participate were given a screening examination. This included a medical history, physical examination, evaluation of Tanner stage (40), blood collection for glucose and iron concentrations, and fecal and urine screening for acute infections. Children were excluded from the study if they were taking any medication, if their Tanner stage for ≥1 criterion was >1, or if we identified any past medical problems that might influence current health status or metabolic condition (such as hyperthyroidism or chronic anemia). Any child who had an acute health problem, such as an acute intestinal or urinary infection, was treated according to the usual procedures of the São Paulo Hospital and began the study only after successful completion of treatment.

Ethical approval for the study was obtained from the Federal University of São Paulo Hospital and the Human Investigation Review Committee at the New England Medical Center, Tufts University. Written informed consent was obtained from both the subjects and their parents before the study began.

Study protocol

The children were admitted to the metabolic research unit of the Center for Nutritional Recovery and Education at the Federal University of São Paulo at 0700 on study day 1 and were returned to their homes at 2100 on day 3. They were admitted in groups of 4; 2 stunted children and 2 control children were admitted together when possible. Continuous daytime supervision was provided by investigator DJH and 2 assistants and nighttime supervision was provided by a nurse. Throughout the 3 d, subjects consumed only food and drinks prepared by the research center and refrained from vigorous physical activities.

Resting energy expenditure (REE) was measured in the fasted state 12 h after the evening meal on all 3 mornings (one 30-min measurement and two 15-min measurements) under thermoneutral conditions by indirect calorimetry with a DeltaTrac metabolic monitor (SensorMedics, Yorba Linda, CA). Subjects were instructed to relax and avoid hyperventilation, fidgeting, and sleeping during the measurements and were allowed to watch taped movies if they so desired. The calorimeter was calibrated with a standard gas mixture (96% O₂ and 4% CO₂) before each measurement and alcohol burn tests were conducted every 2 wk to ensure the accuracy of the calorimeter. Values for REE were determined by using the mean volumes of oxygen consumed (V̇O₂) and carbon dioxide produced (V̇CO₂) for each measurement (41).

The thermic effect of feeding (TEF) was measured over a 3-h period on either day 2 or day 3 after the measurement of REE. For the TEF measurement, subjects consumed a standard breakfast (bread with margarine and chocolate milk) that supplied 42 kJ (10 kcal) per kg body wt. All the children received the same proportions of the different foods. The children were instructed to consume their meal within 5 min and the measurement began 15 min later. Energy expenditure was measured for 15 min of every one-half hour during the measurement period. Urine was collected during a 24-h period that included the TEF measurements. Urine was analyzed for nitrogen excretion by using a modification of the Kjeldahl technique that involved microwave digestion of the samples (Kjelfast; CEM, Matthews, NC). The TEF was calculated as the energy expenditure increment over fasting at baseline and was expressed as a percentage of ingested energy. Fat oxidation was calculated from V̇O₂ and V̇CO₂ during the fasting and postprandial measurement periods and from urinary nitrogen excretion, with the assumption that nitrogen excretion was steady over the 24-h collection period.

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of the study children and parents</th>
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<tbody>
<tr>
<td>Control group</td>
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<tr>
<td><strong>Children</strong></td>
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<td><strong>Fathers</strong></td>
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<td>Height (cm)</td>
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<td>BMI (kg/m²)</td>
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<td><strong>Mothers</strong></td>
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<tr>
<td>Height (cm)</td>
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<td>BMI (kg/m²)</td>
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* ± SD. For control group, n = 50 children, 16 fathers, and 20 mothers. For stunted group, n = 28 children, 10 fathers, and 18 mothers. Significantly different from control group, P < 0.001 (Student’s unpaired t test).
RESULTS

The control and stunted groups were not significantly different in age and WHZ but, as intended, the control group had greater height, HAZ, and body weight than did the stunted group (Table 1). The 2 groups did not differ significantly in percentage body fat or lean body mass. In the subset of parents whose anthropometric measurements could be obtained (n = 64), there were no significant differences in either height or body mass index (BMI; in kg/m²) between the groups (Table 1).

REE and TEF data are shown in Table 2. Compared with control children, stunted children had lower unadjusted REE and higher REE/kg body wt. However, after adjustment for lean body mass by multiple linear regression (45), REE did not differ significantly between the groups. TEF was also not significantly different between the groups. TEF data are summarized in Table 2 and the time course of TEF over the 3-h measurement is shown in Figure 1. The possibly unusual pattern of TEF (specifically, the relatively low value at 60 min after the meal) could not be explained on the basis of any specific study procedures.

Data on fasting and postprandial RQ and substrate oxidation are shown in Table 3. The fasting RQ and nonprotein fasting RQ were significantly higher in the stunted group than in the control group. These differences remained even when children who had an RQ > 1.00 (n = 5) were excluded from the analyses or when the previous day’s energy intake and food quotient (calculated ratio of VO₂ to VCO₂ during complete combustion of consumed foods) were examined as confounding variables in multiple regression models. The control group also oxidized a significantly lower percentage of their fuel mix as carbohydrate and a significantly greater percentage as fat than did the stunted group.

Concerning postprandial fat oxidation, mean postprandial RQ was not significantly different between the 2 groups when averaged over the 3-h experimental period (Table 3), and consequently, mean postprandial rates of fat and carbohydrate oxidation were also not significantly different. However, as shown in Figure 2, RQ tended to remain elevated in the stunted group compared with the control group. Consequently, during the postprandial phase, the control group had a significantly lower RQ at 30 min (assessed statistically as described in the Statistical Analysis section; Figure 2). Also note that postprandial changes in RQ from baseline did not differ significantly between the 2 groups. We interpret these observations to indicate that fasting RQ was significantly higher in the stunted group, but the change in RQ with feeding did not differ between groups.

![Figure 1](https://example.com/figure1.png)
influence fat oxidation to different extents. Whether different underlying causes of nutritional stunting may
effects. Further studies will be needed to address the question of
ciciency of a specific nutrient such as zinc) might have different
multiple nutrients including energy as opposed to chronic defi-
different underlying causes (for example, chronic deficiency of
population. Therefore, we cannot exclude the possibility that dif-
occurred. By selecting children for each group from the same
weight gain rather than factors apparent only after weight gain
measure factors contributing to an underlying susceptibility to
stored. Thus, impaired fat oxidation will tend to cause increased
fat deposition over time. In theory, impaired fat oxidation will
accelerate fat deposition particularly quickly when a high-fat
diet is consumed, because the excess fat intake will be deposited.
With regard to this possibility, we previously obtained prelimi-
data suggesting that stunted children gain weight over time at
an accelerated rate when they consume a high-fat diet (14).
It can be speculated that in nutritionally stunted children, long-
term adaptations to undernutrition that affect enzyme and hor-
function may underlie impaired fat oxidation. For example,
chronic undernutrition is accompanied by reduced concentra-
tions of insulin-like growth factor I (IGF-I) (14, 47). Because
IGF-I increases the activity of hormone-sensitive lipase to lipoly-
topic hormones (48, 49), any reduction in IGF-I may also result in
decreased fat oxidation (50). In addition, studies in rodents have
suggested long-term effects of litter size (a classic tool for study-
ing the effects of early nutrition) on enzymes involved in carbo-
hydrate and fat oxidation 20 wk after weaning (17). For example,
20-wk-old rats undernourished at birth had elevated concentra-
tions of gluconeogenic enzymes, which might promote increased
carbohydrate oxidation relative to fat oxidation (17).
Although we studied children living in Brazil, it is important
to note that children in other countries are susceptible to under-
nutrition and stunting also: ≈250 million children worldwide
are thought to suffer from malnutrition (51) and 5–10% of chil-
dren in the United States have been classified as stunted (52). In
developing populations, nutritional stunting is primarily related
to undernutrition, but in developed populations it is more com-
monly associated with a range of common childhood problems,
including severe burns (53), excess fruit juice consumption (54),
fear of obesity (55), and low social class (56). Most previous
reports on stunting did not provide information on body fatness,
but stunting in children with previous burn injuries was associ-
ated with a disproportionate gain in weight relative to height 3 y

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\begin{array}{ccc}
\text{Control} & \text{Stunted} \\
(n = 30) & (n = 28) \\
\hline
\text{Fasting} \\
\text{RQ} & 0.89 \pm 0.007 & 0.92 \pm 0.009^2 \\
\text{Nonprotein RQ} & 0.90 \pm 0.009 & 0.94 \pm 0.009^2 \\
\text{Carbohydrate oxidation} & 66 \pm 2 & 75 \pm 2^2 \\
\text{Fat oxidation} & 34 \pm 2 & 25 \pm 2^2 \\
\text{Postprandial} \\
\text{RQ} & 0.93 \pm 0.007 & 0.94 \pm 0.007 \\
\text{Cumulative carbohydrate oxidation} & 80 \pm 3 & 84 \pm 3 \\
\text{Cumulative fat oxidation} & 20 \pm 2 & 16 \pm 3 \\
\end{array}
\]

\(^1\text{SEM.} \quad ^2\text{Significantly different from control group (Student’s unpaired t test):} \quad ^3P < 0.05, ^4P < 0.01.

\textbf{DISCUSSION}

Impaired fat oxidation was shown previously to be a risk fac-
tor for excess weight gain in several populations known to be
susceptible to obesity, including Pima Indians, previously
obese women who had completed a weight-reduction program,
and middle-aged men (28–32). In the present study, we found
that nutritionally stunted children had measurably impaired fat
oxidation compared with nonstunted control children living in
the same environment. Specifically, stunted children had signifi-
cantly higher RQs and lower fat oxidation in the fasting state
and 30 min after a meal (subsequent postprandial measure-
ments remained higher but not significantly so). This finding of
reduced fat oxidation in the fasting and early postprandial
states may help to explain previous observations (11–13) of
increased prevalence of overweight among stunted adolescents
and adults in developing countries, because fat that is not ox-
dized must be stored. Our findings also add to the literature
suggesting that diet early in life has a significant effect on later
metabolism and health (24, 26, 27).

Several aspects of the study design were critical to our inter-
pretation of the results obtained. First, we used an inpatient
protocol in which all food was provided to the children. This was
important because dietary composition on the day preceding the
measurement can influence fasting fat oxidation (46). In addition,
none of the children were obese yet, which enabled us to
measure factors contributing to an underlying susceptibility to
weight gain rather than factors apparent only after weight gain
has occurred. By selecting children for each group from the same
environment and ensuring that the groups had values for parental
height and BMI that were not significantly different, we also
reduced the number of factors other than nutritional stunting that
could explain our results. Note that we were unable to distingui-
sh between different causes of nutritional stunting in this
population. Therefore, we cannot exclude the possibility that dif-
derent underlying causes (for example, chronic deficiency of
multiple nutrients including energy as opposed to chronic defi-
cency of a specific nutrient such as zinc) might have different
effects. Further studies will be needed to address the question of
whether different underlying causes of nutritional stunting may
influence fat oxidation to different extents.

Although the mechanisms by which chronic undernutrition
leading to stunting causes an alteration in fat oxidation are not
known, there are several potential explanations. At the level of
fat oxidation versus storage, fat that is not oxidized must be
stored. Thus, impaired fat oxidation will tend to cause increased
fat deposition over time. In theory, impaired fat oxidation will
accelerate fat deposition particularly quickly when a high-fat
diet is consumed, because the excess fat intake will be deposited.
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tions of gluconeogenic enzymes, which might promote increased

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\text{FIGURE 2. Mean (±SEM) fasting (0 min) and postprandial respira-
tory quotient in stunted and control children. *Significantly different}
\text{from the stunted group, } P < 0.05. \text{ The average respiratory quotient did}
\text{not differ significantly between the 2 groups.}
\]
after the burn accident (53). Also, short adults of low social class had a significantly greater BMI than did taller individuals of higher social class in England (56) but not in France (57).

In summary, this study showed that nutritionally stunted children have impaired fat oxidation compared with nonstunted control children from the same environment. This finding suggests that stunted shantytown children are at increased risk of obesity and may gain weight over time when food supplies become sufficient to allow ad libitum consumption. Our results may therefore help to explain the previous finding of an increased prevalence of obesity among stunted children and short adults in developing countries.

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REFERENCES