Results and Implications of the INCAP Follow-up Study[1,2]

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ABSTRACT This article is a critical synthesis of 12 papers included in this supplement. The set deals with the short- and long-term effects of improving nutrition in Guatemalan villages characterized by deficient diets, high rates of infection and pronounced growth retardation in the first 3 y of life. The data reviewed come from two studies carried out over two decades: the Institute of Nutrition of Central America and Panama (INCAP) longitudinal study (1966–1977) and its follow-up (1988–1989). The longitudinal study included a nutrition intervention that improved the energy and nutrient intakes of women and preschool children. Its effects included improved birthweights, reduced infant mortality rates and improved growth rates in children < 3 y of age. Growth rates from 3 to 7 y of age, similar to those of well-nourished children, were not affected by the intervention. The follow-up study was conducted when the subjects were 11–27 y old. Among the long-term effects found were greater stature and fat-free mass, particularly in females, improved work capacity in males and enhanced intellectual performance in both genders. The nutrition intervention did not, on the other hand, accelerate maturation during adolescence, as measured by skeletal age or age at menarche. It is concluded that improved nutrition in early childhood has important long-term effects in the adolescent and adult. J. Nutr. 125: 1127S–1138S, 1995.

INDEXING KEY WORDS:

- *nutritional supplementation* • *adolescence*
- *malnutrition* • *growth and development*

This article is an overview of papers included in this volume, with emphasis on the main findings and policy implications of the Institute of Nutrition of Central America and Panama (INCAP) follow-up study (1988–89). A previous set in the Food and Nutrition Bulletin (Vol. 14, number 3, 1992) concentrated on the study which preceded the follow-up, namely the INCAP longitudinal study (1969–77).

To provide readers with the context necessary to interpret the findings of the follow-up study, the first three papers of this volume (Habicht et al. 1995, Martorell et al. 1995a, Schroeder et al. 1995) present essential information from the earlier INCAP longitudinal study, the next seven papers deal with the follow-up study and the last one is a comparison of our findings to those of the Nutrition Collaborative Research Support Program (CRSP) studies (Allen 1995).

This effort is an attempt to provide a critical summary of the findings and is guided by the following questions: What has been learned from the INCAP studies that is important? Are these results believable and internally consistent? What lessons for policies and programs can be drawn from these results? The first section is a discussion of the original INCAP longitudinal study and its results and is followed by sections dealing with design and analytic issues and with the key findings of the follow-up study. The article ends by addressing the program and policy implications of the results of the INCAP and follow-up studies.

The INCAP Longitudinal Study (1969–77)

The villages. The studies took place in four small villages of eastern Guatemala. When chosen in 1968, two had ~900 inhabitants each and two had ~500 each but had grown to 1,200 and 800 by 1975, respectively. Mean household incomes per year in these villages, where the primary occupation was subsistence agriculture, ranged from US $291 to $463 in 1975. Maternal literacy ranged from 25 to 40% in 1967, and 10 years later, this had risen from 35 to 50%. Although all villages had schools when the study began, it was not until around 1980 that instruction

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up to 6 y of elementary schooling was offered. Electricity became available in the midst of the study in the two small villages and, in the 1980s, in the larger ones. Most families obtained water from wells or rivers and few had latrines. Typical houses were small, one to two rooms, and made of adobe. Driving into these villages was difficult, particularly during the rainy season, but one village close to the highway was more accessible. The dietary staples, as in most of rural Guatemala, were corn and beans, complemented occasionally by small amounts of meat and by fruits and vegetables when in season. Additional details are provided by Bergeron (1992), Engle et al. (1992) and Martorell et al. (1995a) but enough information has been given to illustrate the setting of poverty and rural isolation in which the study took place.

The supplementation program. The longitudinal study was designed to test the hypothesis, in vogue in the 1960s, that malnutrition retards mental development. Researchers operationalized the study as an assessment of the impact of significantly improving protein intakes in mothers during pregnancy and lactation and in children during the first 7 y of life. The treatment was a drink called Atole, rich in high quality protein, the nutrient then thought to be the main constraint to nutrition in developing countries. However, the Atole contributed much more than protein because it is impossible to provide a food-based supplement that is rich in it without simultaneously providing energy, as well as important amounts of some vitamins and minerals. There were additional considerations about the treatment. The researchers feared that the setting in which the Atole was made available, an attractively painted large room with blue tables and chairs set about and with uniformed attendants serving the Atole in brightly colored cups, would be conducive to considerable social interactions among consumers that, in turn, might affect psychological development in the target sample, independent of the nutritional effects of the Atole. Consequently, a protein-free beverage called Fresco was provided under the same set of conditions as the Atole in two villages to serve as control to the two receiving Atole. The careful almost fastidious recording of attendance and amount of supplement provided (subjects were free to drink as many cups as desired, each containing 180 mL) and of the measurement of leftovers was a feature in both Atole and Fresco villages. Attendance and consumption records were kept for pregnant and lactating women and for children ≤7 y; although all villagers were free to attend, the participation of men, older women and children > 7 y old was unrecorded.

Four villages were selected in 1969 for the study. The pair of large villages was randomized to receive Atole or Fresco, as was the pair of small villages. Although great care was taken to choose pairs of villages that were similar to each other, important differences existed then or surfaced later in nutrition and health as well as in social, educational and demographic conditions, but these differences do not favor any village systematically; rather, there is considerable variability in the comparative rankings by village depending upon the aspect considered (Bergeron 1992, Engle et al. 1992, Martorell et al. 1995a).

The Fresco was devoid of protein and because empty calories were thought to be potentially harmful, it contained only enough sugar and flavoring to make a palatable refreshing drink. A number of vitamins (thiamin, riboflavin, niacin, vitamin A, ascorbic acid) and minerals (iron, fluoride) were added to the Fresco early in the study to make its composition similar to that of the Atole except with regard to protein; the obvious differences in terms of energy, which favored the Atole, were not thought to be nutritionally significant at the time. The Atole, but not the Fresco, also contained calcium and phosphorus, as well as other nutrients whose presence has gone unrecognized in publications about the study, such as zinc, vitamin B-6, folacin and B-12 (Allen 1995). The content per cup of the Atole was 11.5 g of protein and 163 kcal/682 kJ per cup (180 mL) and of the Fresco was 0 g protein and 59 kcal/247 kJ per cup. Both the Atole and Fresco drinks were similar to local preparations and both were liked, but patterns of intake differed. In mothers, attendance was similar but the Fresco was consumed, on a volume basis, at about twice the rate of the Atole (Delgado et al. 1982). This is understandable in that the Fresco was light and thirst quenching and the Atole was thick and served hot. Patterns in children were much different (Schroeder et al. 1992). Attendance below 3 y of age was greater in Atole villages as was the volume consumed; after 3 y, attendance was similar but the volume consumed was greater in Fresco villages (**Fig. 1, Fig. 2**).

The nature of the intervention. What was the nature of the intervention? This can be answered in

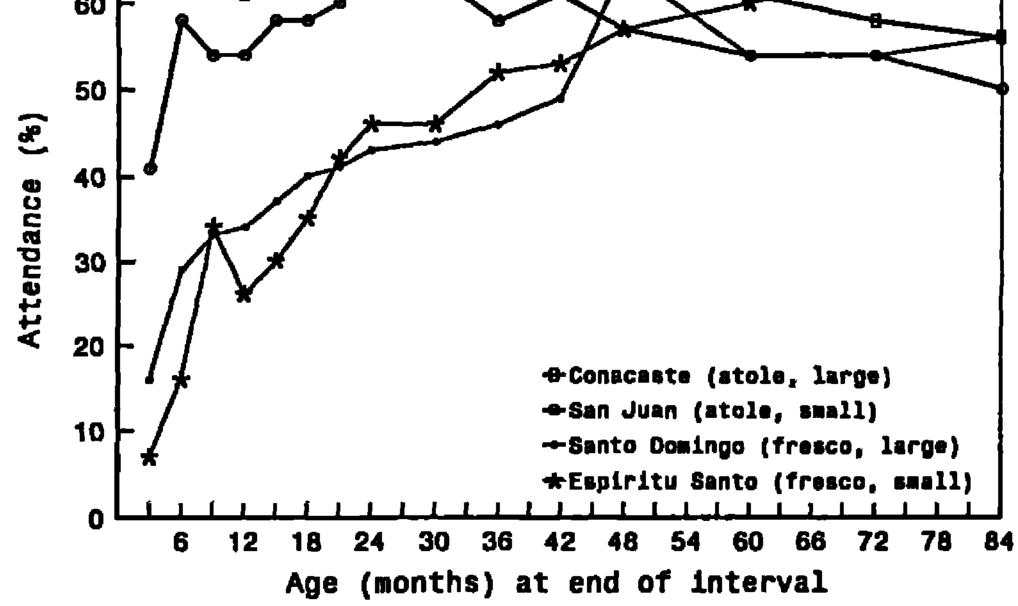

FIGURE 1 Attendance of participants at the feeding center (percentage of days in interval) by age and village. From Schroeder et al. 1992.

the narrow sense in terms of improvements in nutrient intakes in mothers and children. In mothers, average intakes of energy from the supplements during the entire pregnancy were 107 kcal/448 kJ per day in Atole villages and 81 kcal/339 kJ per day in Fresco villages (Delgado et al. 1982). Thus, the greater consumption of the Fresco nearly made up for its lower energy concentration. Average daily protein intakes from the Atole were ~7.5 g; the Fresco had no protein. Intake of a number of vitamins and minerals common to both drinks was about twice greater in Fresco villages, because Fresco was consumed that much more and the concentration was similar in Atole and Fresco villages. The rate of replacement of home diet is not known with precision but is estimated to have been 22% for energy (Habicht et al. 1995).

In children 15–36 mo, average total energy intakes per day (i.e., home diet and supplement combined) were greater in Atole compared with Fresco villages by ~101 kcal/423 kJ in boys and 89 kcal/372 kJ in girls; this is equivalent to ~11% of the total intake in Fresco villages. Comparisons of total intake of protein favored Atole boys by 8.6 g and Atole girls by 8.8 g, equivalent to ~40% of the intake in Fresco villages (**Table 1**). Children in Atole villages, because they ingested significantly greater volumes of supplement from 15 to 36 mo of age than children in Fresco villages did (Fig. 2), also had significantly greater intakes of many vitamins and minerals.

The preceding makes it clear that the intent in 1969 of creating a contrast between village types in terms of protein was realized but along with other effects. Supplement intakes during pregnancy in Atole women were improved substantially in terms of protein, but both Atole and Fresco women received nearly similar amounts of energy from the supplements and the Fresco group ingested greater amounts of a number of vitamins and minerals. In children < 3 y of age, intakes of protein were increased in Atole villages but so were those of energy, vitamins and minerals. In children 3–7 y of age, protein intakes were increased in Atole villages, but despite the greater volume of Fresco consumed as children got older, the energy consumed from the Fresco was still less than that from the Atole, but the gap narrowed considerably as children neared 7 y of age (**Fig. 3**). Finally, the contribution from the supplements of those vitamins and minerals found in equal concentrations in both drinks was greater from Fresco than from Atole after ~4 y of age when more of the Fresco began to be consumed.

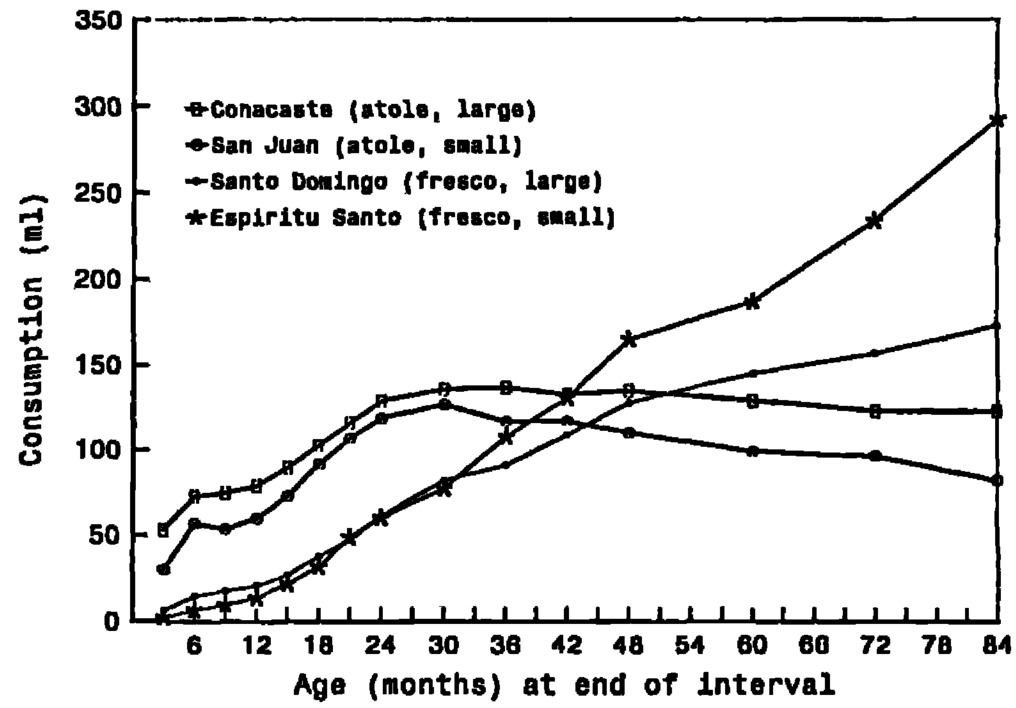

FIGURE 2 Mean volume of supplement consumed per day by age and village (nonparticipants included). From Schroeder et al. 1992.

TABLE 1

Contribution of the supplements to total energy and protein intakes in children 15–36 mo of age[1]

	Males		Females		
	Atole (n = 128)	Fresco (n = 135)	Atole (n = 118)	Fresco (n = 104)	Pooled SD
Energy, *kcal/d*					
Home diet	785	814	718	756	213
Supplement	156	26[a]	150	23[a]	79
Total Intake	941	840[a]	868	779[b]	226
Energy, *kJ/d*					
Home diet	3,284	3,406	3,004	3,163	891
Supplement	653	109[a]	628	96[a]	331
Total Intake	3,937	3,515[a]	3,632	3,259[b]	946
Protein, *g/d*					
Home diet	20.1	22.5	19.3	21.0	5.9
Supplement	11.0	0.0[a]	10.5	0.0[a]	5.4
Total Intake	31.1	22.5[a]	29.8	21.0[a]	7.5

[1] Home diet values are averages of as many as eight recall surveys conducted at 15 mo and every 3 mo thereafter until 36 mo (adapted from Martorell, 1982).

[a] $P < 0.001$.

[b] $P < 0.01$.

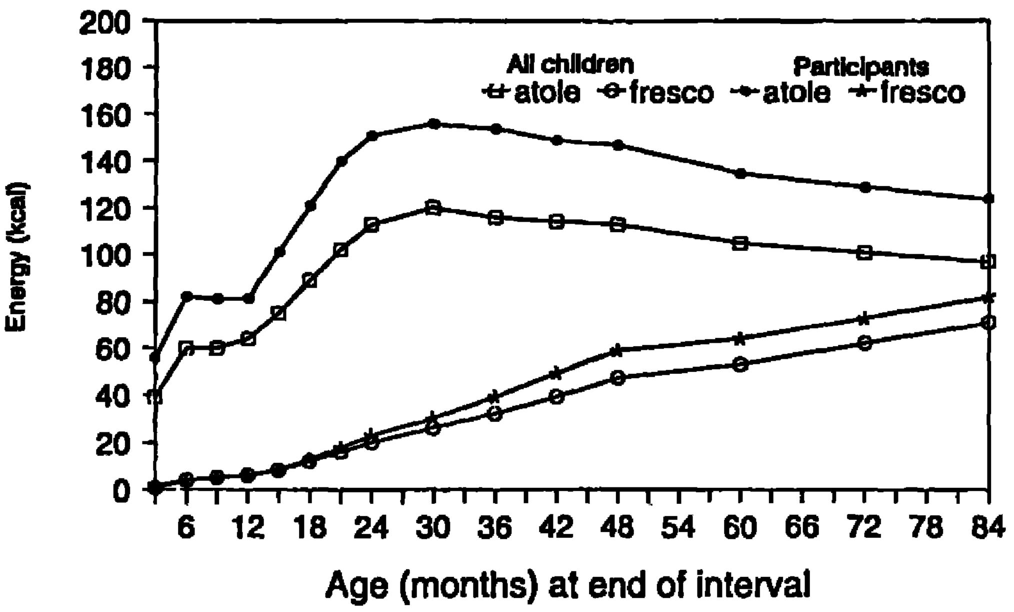

FIGURE 3 Mean energy intake per day from supplement by age and supplement type (with and without nonparticipants). From Schroeder et al. 1992.

Was the Fresco, as originally intended, an adequate control for the socialization effects that might result from the social interaction at the feeding centers? The answer appears to be a qualified yes in that patterns of attendance were similar in Atole and Fresco villages in the case of pregnant women and older children but not in young children. Fortunately, attendance and consumption of supplement were measured, permitting researchers to control for participation in contrasting Atole and Fresco communities, particularly important in the analyses of behavioral outcomes (Pollitt et al. 1995). Living closer to the feeding center and being from a larger family predicted participation in children in both village types; however, children of poorer families had greater participation in the supplementation program only in Atole villages (Schroeder et al. 1992). Failure to control for socioeconomic status in analyses of the relationship between Atole intake and outcomes might therefore bias the results against the hypothesis that consumption leads to improved status.

In addition to the supplementation program, INCAP established a medical care program in all four communities (Martorell et al. 1995a). These services were provided by auxiliary nurses under the careful supervision of a physician. A range of curative services, with appropriate referral in case of complications, was given. Also, periodic examinations during the prenatal period and during early childhood were carried out. Vaccines were administered in these visits. These efforts, although important, fell short of the ideal in that community nutrition and health education were not provided outside the context of medical care visits. Also, there were no programs implemented in environmental sanitation, formal education or economic development.

Finally, another component of the intervention, the very presence of INCAP investigators asking questions and examining women and children, must have had some unspecified effects, but these, because of careful rotation among personnel and similar research activities in all four villages, cannot bias the comparison of Atole and Fresco villages (Habicht et al. 1995).

In summary, the nature of the intervention is a contrast between villages receiving different types of supplements but identical medical services and similar but unintended effects of having a research team present for about 8 years. In children *15–36 mo of age*, exposure to different supplements increased total energy intakes by 11% and total protein intakes by 40% in Atole villages relative to Fresco villages. Also, total intakes of many vitamin and minerals also were substantially greater in Atole compared with Fresco villages. Because of the uncertainty about the energy requirements of children, it is impossible to say how far the extra 100 kcal/418 kJ per day went toward meeting needs, but it is unlikely that adequate levels were reached. Average energy intakes of Atole and Fresco children, combining home diet and supplement, were ~93 and 83 kcal/kg (389 and 347 kJ/kg) at 24 mo of age, respectively, compared with estimated requirements of ~110 kcal/kg (460 kJ/kg) given by FAO/WHO/UNU (1985). This would mean that children in Atole and Fresco villages had intakes equivalent to 85% and 75%, respectively, of the requirement. Allowances for catch-up growth, usually taken into account by using ideal rather than actual body weights, would of course increase the apparent energy gap substantially. For protein, on the other hand, average intakes exceeded allowances even before considering the contribution of the Atole; average total protein intakes were 3.1 and 2.2 g/kg in Atole and Fresco villages compared with the safe level of 1.8 g/kg at 24 mo of age (adjusted conservatively for an amino acid score of 60 and a digestibility score of 85).

Approaches to analyses. A meta-analysis of nutrition interventions during pregnancy and birthweight excluded the findings of the INCAP longitudinal study from all consideration (Kramer, 1993). The reason given was that the analyses were not carried out according to the randomized design.

The randomized design calls for village to be the unit of analysis. Because the comparison of village means involves only two Fresco and two Atole villages, statistical power is extremely low (Habicht et al. 1995). It is doubtful that those who designed the study intended for it to be analyzed in this manner. If the randomized design is used to test for birthweight differences, no effect is found; mean birthweights in Atole are slightly greater than those in Fresco villages, but this small difference is not statistically significant (3077 ± 334 and 3027 ± 461 g, respectively; Delgado et al. 1982). As reviewed earlier, the mean intake of energy from the supplements during pregnancy also was slightly greater in Atole than in Fresco villages. It turns out that energy intakes from the supplements, irrespective of whether accompanied by protein, were related to birthweight (Habicht et al. 1995). The similarity in the dose-response relationship in Atole and Fresco samples, when expressed in terms of energy, implies that vitamins and minerals present in both drinks in equal concentrations could not account for the findings. If this were the case, regression coefficients would be more than twice larger for Fresco, when expressed per units of energy, and similar to those for Atole, when given per units of volume. Thus, because energy turned out to be limiting for birthweight and because both the Atole and Fresco contributed nearly equal amounts of energy during pregnancy, the randomized design became inappropriate.

The reasons for abandoning the randomized design in the analyses of birthweight are justified but the credibility of the results, as exemplified by Kramer's decision to exclude the study, suffers. However, others have given considerable importance to the individual level analyses of supplement intake and birthweight, giving due weight to their internal consistency and the careful efforts to control for confounding. Thus, the finding that 20,000 kcal/83,684 kJ provided during pregnancy will reduce the prevalence of low birthweight by half (Lechtig et al. 1975) has helped to justify maternal nutrition programs worldwide.

The randomized design is used by Habicht et al. (1995) to analyze the effects of exposure to Atole on attained lengths at 3 y of age. Baseline values of length at 3 y of age in 1968 (before the study) are used to estimate, for each of the four villages, the differences in length with respect to values for children born after the study began in 1969. Using village means, Habicht et al. (1995) estimated that the Atole sample grew ~2.5 cm more than children in Fresco villages ($P < 0.005$, $df = 2$). This may be a conservative estimate of the impact of Atole because children in Fresco villages grew ~0.5 cm more compared with baseline values, perhaps because of the small amounts of energy and other nutrients received from the Fresco and/or because of the medical care program, among other possible reasons. It should be noted that the small degree of change in Fresco villages implies that the medical care program and energy supplementation during pregnancy appear to have had little impact on *postnatal growth*.

An extension of the randomized design also has been used by Martorell (1992) in examining time trends in severe stunting (i.e., lengths that are ≥3 SD below the reference mean) in Fresco and Atole villages. The prevalence of severe stunting was ~45% in both Atole and Fresco villages at the beginning of the study in 1969 and declined at the end of the study, in 1976–77, to <20% in Atole villages but remained at about the same level in Fresco villages. A logistic regression of trends by village with treatment, sex and year as independent variables and village as the unit of analysis showed a statistically significant decline only in Atole villages ($P < 0.01$).

Also, a village level analysis has been used in assessing changes in infant mortality, using data collected through retrospective women's life histories (Rose et al. 1992). Relative to baseline levels in 1949–68, infant mortality rates declined by 66% in Atole villages and by 24% in Fresco villages, but the rates of decline were not significantly different from each other ($P > 0.05$). Data collected in three of the villages considered for selection but not included in the longitudinal study showed a rate of decline of 19% over the same period, presumably reflecting general trends in rural Guatemala. The rates of decline in Atole villages, but not those in Fresco villages, were significantly different ($P < 0.05$) from those observed in these three undisturbed villages.

Thus, despite low statistical power, analyses using the randomized design have demonstrated a significant impact of Atole ingestion on physical growth at 3 y of age and on infant mortality. In both these situations we had baseline data available that permitted a before/after design, thereby increasing precision of the estimate of change in each village. We lack baseline data for birthweight (never collected) and for all the psychological variables in the infant and preschool batteries (some data apparently were collected but these cannot be found despite careful searches).

Instead of the randomized design, analyses of the psychological data, as indeed many of those dealing with physical growth, have used the individual as the unit of analysis, which vastly increases statistical power. These analyses are of two types. One compares means in Atole villages to those in Fresco villages, in analyses of covariance that adjust for potentially confounding factors such as socioeconomic status, with the degrees of freedom determined by the number of individuals and the model used. A second type of analysis examines the dose-response relationship between supplement intake and outcomes, controlling for potentially confounding factors.

These analyses do not have the rigor of the randomized design, which incorporates the potential effects of confounding factors in the design (Habicht et al. 1995). Instead, the individual level analyses deal with confounding through the analyses. Although previous analyses of our data almost always have included adjustment for potentially confounding factors, this was necessarily limited to those aspects measured in the study and incorporated in the analysis.

Follow-up study (1988–89)

Design and analyses issues. The follow-up study was a cross-sectional evaluation of former participants of the INCAP longitudinal study of 1969–77 (Martorell et al. 1995a). The main hypothesis was that the nutritional improvements in the critical period of gestation and the first 3 y of life ultimately produce adolescents with a greater potential for leading healthy productive lives. Anyone ≤7 y when the study began or who was born into the study was included in the target sample. Migrants were measured as well but, because of costs, only those moving to certain urban centers were included. The main areas of data collection were anthropometry, medical examinations, hand-wrist X-rays, blood samples (for iron measures), psychological tests, retrospective life histories and work capacity. About 73% (1574/2169) of subjects in the four study villages were included in the follow-up. Coverage was 41% (296/727) in migrants and 89% (1278/1442) in nonmigrants.

The follow-up was an ambitious attempt, the first of its kind, to look at the long-term effects of a nutrition intervention in a developing country. The range of outcomes measured was broad and was meant to provide indicators of human function across a range of domains. The follow-up adds new knowledge because it extends the usual horizon for evaluating nutrition interventions to tap functions and abilities in the adolescent and young adult that are not present or not yet developed in their entirety in young children. At the same time, the follow-up has important design limitations that limit the range of possible analyses and their credibility. These limitations are discussed below.

At the time of the follow-up, the subjects ranged from ~11 to 27 y of age. Subjects were exposed to supplementation over a wide range of ages and for varying durations, from those who were 7 in 1969 when the study began (exposed for 9 y from 7 to 16 y of age) to those born in 1977 when the study ended (exposed only during infancy). Ages at exposure and years of exposure by year of birth are given by Khan et al. (1995). Our ability to study the differential impact of supplementation at various ages is limited by the fact that recording of ingestion of supplement and measurement of other outcomes in the INCAP longitudinal study were carried out only until 7 y of age.

The main hypothesis of the follow-up study states that nutritional improvements during pregnancy and the first 3 y of life should result in improved outcomes in adolescence. Most of the papers test this hypothesis by comparing outcomes in Atole and Fresco subjects born on or after March 1, 1969 to February 28, 1974 (designated as Cohort 2 in Martorell et al. 1995a). This is the group exposed during what we have called the critical period (pregnancy and the first 3 y of life). The expectation is that examination of effects in this group is more likely to uncover differences between Atole and Fresco. This approach, to be complete, should include comparison of results for this cohort to those observed in cohorts exposed to supplementation at other periods, but this has been done only in some areas (Haas et al. 1995; Khan et al. 1995). Because of the lack of baseline data (i.e., pre-1969 data) on adolescent outcomes, the randomized design has not been used in analyzing the results of the follow-up.

The basis for designating pregnancy and the first 3 y of life as the critical period comes from the analyses on birthweight reviewed above, from results presented by Schroeder et al. (1995) and Martorell et al. (1995b) as well as from other considerations. Adolescents and adults in our sample are short in height compared with reference values but growth rates are retarded only in the first 2–3 y of age. This is a time when nutritional needs (per kg of body weight) are greater, when growth in length is still rapid, although decelerating, and when diarrheal diseases are more common. The above are some of the reasons that might explain why a striking relationship between supplement intake and growth is found in the first 3 y of life, but not from 3 to 7 y of age. Pollitt et al. (1995) assessed effects on behavioral outcomes and reduced the upper bound of the critical period from 3 to 2 y of age, on the basis that pregnancy and the first 2 y are periods of marked brain development and perhaps the times most sensitive to the effects of nutrition. The group considered by Pollitt includes all Cohort 2 subjects as well as some Cohort 1 subjects, specifically those fully exposed to the nutritional intervention during pregnancy and the first 2 y of life but with variable exposure from 24 to 36 mo of age; the birthdates for the cohorts are given by Martorell et al. (1995a).

The analyses that contrast Cohort 2 subjects in Atole and Fresco villages control for potentially confounding factors but the models used in the various papers rarely are identical. This reflects in part the diverse nature of the outcomes analyzed (e.g., maximal oxygen consumption and reading achievement), which requires a different set of covariates, and the equally varied disciplinary approaches of the various members of the research team.

A major difficulty in the analyses was the need to control for maturation and/or age because many of the subjects were adolescents. This increased the complexity of the models and complicated the interpretation of the results, as exemplified by the analyses of body size by Rivera et al. (1995). Adolescent males in Fresco villages were taller than their counterparts in Atole villages but they were also older by 0.5 y; controlling for this difference reversed the trend and made Atole males taller, as predicted. At the same time, the fact that adolescents were included in the follow-up study permits analyses of effects on maturation per se (Pickett et al. 1995) and on growth during adolescence (Martorell et al. 1995b); these are significant contributions to the literature on adolescence, a group largely ignored in previous studies in developing countries.

A related problem is that effects of the nutrition intervention on productivity, measured in terms of goods produced, income or their proxies, could not be studied adequately in a young sample. Rather, the young age of the sample limits one to study potential in human capital through variables such as body size and composition, work capacity and intellectual performance. The issue of the links with productivity is discussed in more detail later.

As reviewed earlier, coverage in the follow-up was ~72%, introducing a source of potential bias in the analyses, an issue addressed generally by Rivera et al. (1992). The availability of data from the preschool period allows examination of characteristics of measured and nonmeasured subjects. Participants in both Atole and Fresco villages tended to be better off in terms of birthweight, physical growth, days ill with diarrhea, home diet and supplement intake. In two economic analyses (Alba 1992, Chung 1992), adjustments were made directly for sample selectivity as recommended by Heckman (1979), but these complex procedures have not been applied in the papers in this series.

Another design limitation of the follow-up study is that it picks up the sample after a hiatus of 11 y (i.e., from 1977, when the longitudinal study ended, to 1988, when the follow-up study began). In some areas the gap has been filled through review of records and through recall interviews or surveys. In this manner we have reconstructed the social and economic development of the communities (Bergeron, 1992), collected information on menarche (Khan et al. 1995) and reconstructed schooling histories (Pollitt et al. 1995). For variables such as diet, morbidity and growth, however, we have no direct measures for these 11 years. In other words, the analyses compare outcomes measured at adolescence or adulthood in Atole and Fresco subjects, often adjusting for covariates in early childhood but not for conditions after the supplementation program ended. This clearly is a limitation. However, socioeconomic status, a variable often included in the models, might be viewed as a proxy for health and diet during the unmeasured period. Also, the period from 7 y of age to adulthood does not appear to be a time of significant stress from the point of view of health and nutrition and omission of information for this period may not be critical in our case. For example, growth in height appears to be similar to that observed in a U.S. reference population beyond the first 3 y of life (Martorell et al. 1995b).

Findings from the follow-up study. What are the key findings from the follow-up study? Are these results internally consistent? Are they of an important magnitude? What potential significance do they have for programs and policies about nutrition? These are some of the questions explored below.

Patterns of growth in height. The follow-up sample was compared with a U.S. reference population and to Mexican-Americans (Martorell et al. 1995b). As young children, Guatemalans grow very poorly relative to both of these U.S. samples. Slightly different characterizations of growth during adolescence are obtained depending upon which is used as the reference, the Mexican-American sample, which is similar in racial ancestry but may not yet show unconstrained growth, or the general U.S. population, largely of European ancestry but probably exhibiting patterns reflective of unconstrained growth potential (i.e., not affected significantly by such factors as infections and dietary deficiencies). Differences in height between Mexican-Americans and the U.S. population are not large but are important. Whereas similar heights are observed up to ~12 y of age, differences begin to appear thereafter; as young adults Mexican Americans are 6 cm shorter, on average, which places them about the 25th percentile of the U.S. reference. Whether these differences reflect genetic or environmental causes is unclear.

Relative to the U.S. reference population, Guatemalans are below the 5th percentile as adults, just as they were as children. Absolute differences in height are slightly greater in adulthood than at 3 y of age (i.e., 13 cm as adults compared with 10–11 cm as children). Thus, growth failure would appear to be confined largely to early childhood. On the other hand, relative to Mexican-Americans, the growth failure of early childhood would appear to be reduced by about one half as a result of gains made up during adolescence. However, regardless of the choice of reference, adolescence, unlike early childhood, does not appear to be a period of constrained growth.

Body size and composition. Adolescents and adults in Atole villages (Cohort 2) were taller, weighed more and had greater fat-free masses compared with subjects in Fresco villages (Rivera et al. 1995). The differences seen at follow-up were shown to have been explained by differences already present at 3 y of age, which in turn have been shown to have been caused by the supplementation program (Habicht et al. 1995). There was some attenuation at adolescence of the differences in length observed at 3 y of age because subjects in Fresco villages grew slightly more from 3 y of age to the time they were measured in the follow-up study compared with subjects from Atole villages. Male subjects grew by 72.1 and 71.3 cm after 3 y of age in Fresco and Atole villages, respectively (difference = 0.8 cm) and by 65.0 and 64.2 cm in Fresco and Atole females, respectively (diff = 0.8 cm). Differences between Atole and Fresco subjects were greater in females than in males both at 3 y of age and at adolescence. At adolescence, the differences in height favoring Atole were 1.2 cm in males and 2.0 cm in females (compared with 2.0 and 2.8 cm, respectively, at 3 y of age) whereas differences in weight were 1.2 kg in males and 2.2 kg in females (compared with 0.8 and 1.2 kg, respectively, at 3 y of age). Atole subjects, particularly females, also had greater fat-free masses; the differences with respect to Fresco subjects being 0.8 and 2.0 kg in males and females, respectively. Thus, we can state that most of the gains achieved by the food supplementation program in early childhood were maintained at adolescence and adulthood.

Maturation. A review of the literature indicates that maturational delays will prolong the period of growth and lead to compensatory growth (Martorell et al. 1994). Thus, the slightly greater growth in height after 3 y of age (i.e., 0.8 cm) in Fresco villages may be due to minor differences in maturation with respect to Atole subjects. As children, subjects in Atole villages were more advanced than those in Fresco villages, as indicated by the greater number of centers of ossification recorded (Martorell et al. 1979) Differences in skeletal maturation at follow-up have been assessed by Pickett et al. (1995), using the Tanner and Whitehouse-2 method in subjects < 18 y (virtually all reached maturity after this age). In Cohort 1, the youngest age group (11–14 y of age), Atole girls were found to be 0.4 y more advanced than those of Fresco; the analyses for girls 14–18 y, corresponding roughly to Cohort 2, were disregarded because many in the sample were approaching skeletal maturity or already had reached it. No differences were found in skeletal maturation between boys in Atole and Fresco villages at either younger (Cohort 1) or older ages (Cohort 2).

Menarche data were collected through recall interviews in 1991 and 1992 in all former participants of the longitudinal study. In analyses that combined all cohorts, mean ages at menarche were 13.75 ± 1.22 y in Atole villages and 13.74 ± 1.36 y in Fresco (Khan et al. 1995). Restricting the analyses to Cohort 2 females showed nearly the same results (13.78 ± 1.28 y for both groups). Using data given in Khan et al. (1995) mean age at menarche for Cohort 1 girls [comparable to the 11–14-y group studied by Pickett et al. (1995)] is 13.45 y in Atole and 13.26 y in Fresco, values not significantly different from each other. The fact that values for Cohort 1 are lower than for Cohort 2 reflects a declining trend in menarche over time.

The skeletal age and menarche results indicate that the food supplementation program had little or no effect on maturation. The results in girls are contradictory (i.e., in Cohort 1, skeletal ages indicate Fresco girls are 0.4 y more retarded than those in Atole but mean ages at menarche are nearly identical in both groups) but the disparity is minor. It is also the case that the population as a whole (i.e., Atole and Fresco combined) does not seem to be markedly delayed. Menarche is perhaps a year or so delayed compared with data from developed countries (Eveleth and Tanner, 1990) and, relative to British children, there is a significant delay in skeletal age of 1.2 y in boys 11–14 y. In boys 14–18 y, skeletal ages differ by only 0.2 y, but this is not statistically significant. Finally, in girls 11–14 y, skeletal age was advanced by 0.2 y, but again, this minor difference was not statistically significant. As noted earlier, maturational delays could not be ascertained reliably in older girls (i.e., 14–18 y).

Thus, unlike some populations in Asia and Africa where the mean age at menarche may be as late as 15 or 16 y, our sample does not appear to be delayed significantly in maturation. Although reference data from a more appropriate group (i.e., upper class subjects from Guatemala City) may clarify the minor discrepancies observed between skeletal age and menarche data, it is unlikely that our conclusions that maturation is delayed at the most by ~1 y and that the food supplementation program had little or no effect on maturation are unlikely to change.

Work capacity. Work capacity in our study was assessed in a subsample as maximal oxygen consumption (VO_2 max). In subjects 14–19 y at follow-up (the age range corresponding to Cohort 2), VO_2 max was significantly greater in males in Atole villages (2.62 and 2.24 L/min for Atole and Fresco samples, respectively). Significant differences also were found, but to a lesser extent, in other cohorts (Cohort 1: 1.70 vs. 1.50; Cohort 3: 2.98 vs. 2.77 L/min; for Atole and Fresco subjects, respectively). Interestingly, the differences remained significant after controlling for body weight and fat-free mass. A dose-response relationship also was found in males in Cohort 2; greater Atole intake was associated with greater VO_2 max. Although Atole females had a higher VO_2 max values in all cohorts, differences with respect to Fresco subjects were less than observed in males and were statistically significant only in Cohort 1 (Cohort 1: 1.40 vs. 1.29; Cohort 2: 1.74 vs. 1.65; Cohort 3: 1.73 vs. 1.63 L/min in Atole and Fresco subjects, respectively).

Given the findings in Rivera et al. (1995) that fat-free mass differences between Atole and Fresco were greater in females than in males, one might have expected that VO_2 max differences between Atole and Fresco would also be greater in females. The reverse was actually found by Haas et al. (1995); the effect found in males was strong and statistically significant whereas that in females was weak for Cohorts 1 and 2 and statistically significant only for the former. One possibility to explain this difference is that the potential for a greater VO_2 max may be unrealized in females because of patterns of physical activity that are much less active than in males, this gender difference increasing with age (Novak et al. 1990). Another potential explanation is that the subsample measured in the work capacity study is not representative of the total sample; this issue was addressed by Haas et al. (1995) who reported no statistically significant differences between samples in supplement ingestion and anthropometric characteristics. However, the direction of the differences in weight and fat-free mass are interesting. Rivera et al. (1995) presented results for the full sample that showed that Atole females have significantly greater fat-free masses than females from Fresco. However, in the subsample, Haas et al. (1995) found that females in Fresco villages have similar weights and fat-free masses compared with subjects in Atole villages, despite being shorter. The reverse was the case in males; differences in weight and fat-free masses between Atole and Fresco subjects actually were greater in the subsample than in the full sample. These observations might appear to provide an explanation, but further analyses suggest otherwise. After controlling for fat-free mass, VO_2 max differences between Atole and Fresco villages continued to be significantly different for males but not females, suggesting that the gender difference in the effect of supplementation is independent of fat-free mass differences between village types. To date, we have no adequate explanation for these differences or for those discussed earlier between the sexes in the response to supplementation in height and fat-free mass.

Bone density. Caulfield et al. (1995) studied the relationship between the supplementation program and bone mineral content, bone width and bone mineral density in adolescence, aspects measured using single-photon absorptiometry at the distal radius. The study sample had less bone mineral content and bone density than German adolescents. Comparison between Atole and Fresco samples showed similar mean values in both sexes, except in females in the case of bone width, where the means were significantly greater for the Atole sample. These village type comparisons, however, did not control for potentially confounding factors. Also, the comparison included all cohorts and may have obscured stronger effects in subjects exposed to the nutrition intervention at particular ages during childhood. In other analyses that used regressions but that also combined all study cohorts, the authors showed that energy intakes from the supplement from birth to 7 y were related positively to the bone mineral outcomes. The relationships were still evident after controlling for age and gender as well as for type of supplement, but socioeconomic status was not included among the potentially confounding variables. When weight and height were included in the analyses, the relationship between energy intakes from supplement and bone density was attenuated and became nonsignificant. Thus, one view of the findings is that the relationship between supplement intake and bone mineral measures was mediated through increased body size. However, the lack of a demonstration of main effects (i.e., differences between Atole and Fresco subjects in mean measures of bone density) and the omission of socioeconomic status in the analyses suggests caution with this interpretation.

Intellectual performance. The effects of the supplementation program on behavioral outcomes were much more evident and consistent in adolescence than in the preschool period. A reanalysis of the 1969–77 data shows that subjects exposed to the Atole during gestation and the first 24 mo of life, when compared with those exposed to Fresco, had improved motor development scores at 2 y and higher scores as well at 4 and 5 y of age in a factor representing perceptual-organizational tests but not in another representing verbal ability tests (Pollitt et al. 1993). At the follow-up, when subjects were 13–19 y of age, Atole exposure was significantly related to tests of knowledge, numeracy, reading and vocabulary and, to a lesser extent, to information processing (Pollitt et al. 1993; Pollitt et al. 1995). No relationship was found on the other hand, in terms of intelligence, assessed with scales A, B and C of the Raven's Progressive Matrices. In older subjects exposed to supplement after 24 mo of age, the pattern of relationships was similar but the number and magnitude of significant associations was greatly reduced, suggesting that exposure before 24 mo was more beneficial. Interactions involving treatment were observed with socioeconomic status and maximum grade attained. Atole exposure, according to Pollitt et al. (1995), acted as a social equalizer, by erasing the relationship between socioeconomic status and performance that was observed in children exposed to Fresco. In terms of the interaction with maximum grade attained, Atole can be characterized as an enhancer of the educational returns to schooling. Atole exposure markedly improved the performance of those with more schooling but had little effect in those with only low levels of schooling.

The findings presented by Pollitt et al. (1995) controlled for sex, age, socioeconomic status, schooling (age at entry, maximum grade attained) and attendance (residual after regressing attendance on consumption). The inclusion of schooling variables in particular was quite important because a number of unadjusted comparisons favored Fresco subjects. Controlling for schooling is justified because of its importance as a determinant of performance and to control for the greater degree of schooling in Fresco villages, a characteristic that predates the beginning of the study in 1969 (Engle et al. 1992).

How can the relatively weak findings observed in the preschool period be reconciled with the more consistent and stronger effects in the follow-up? There is no easy explanation. In a sense, the outcome measures used during the longitudinal study and the follow-up study are not comparable. Unlike variables such as height, there is little assurance in the case of the psychological variables that one is measuring the same underlying aspect or function in young children and in adolescents. In our case, there were no concerted attempts to tap the same constructs at the two periods in life. The longitudinal study battery used adaptations of widely known tests of cognitive development (e.g., embedded figures, verbal inferences) as well as Piagetian concepts (e.g., conservation) whereas the follow-up assessment emphasized psychoeducational tests designed to identify potential to contribute to social and economic development. This led to the inclusion of tailor-made tests of general knowledge, reading and numeracy, all using locally relevant material. The Raven's Test of Intelligence, as noted earlier, was also used in the follow-up.

Pollitt et al. (1993) propose the hypothesis that the nutritional effects of the Atole are mediated through effects on body size, motor maturation and physical activity. For example, smaller children may be treated as if they were younger and low physical activity may limit interaction with the environment. Under this model, effects on intellectual performance are produced slowly through time, as children interact with their family, school and community. Greater effects would be expected in adolescence than in early childhood as, by then, full expression of the psychoeducational growth of subjects would be measurable.

A recent reviewer of these findings is somewhat skeptical of the results because he doubts it is possible to control adequately through confounding for the complexities of the human environment (Dobbing 1994). Astonishingly, he recommends animal experiments because they allow one "to control environmental factors and impose interventions in a structured manner" (p. 602). No doubt the context in which we grow and develop is complex, but animal experimentation, however enlightening it might be, can never be a substitute for human research precisely for this very reason.

Summary and significance of the key findings

The INCAP studies reviewed here provide information about the short- and long-term effects of a nutrition intervention carried out in early childhood. Much of the first part of this paper dealt with the nature of this intervention. Evidence was provided that showed that the supplementation program impacted significantly on energy and protein intakes, raising them by 10 and 40%, respectively, in children 15–36 mo of age, as well as on some other nutrients. Effects on growth were demonstrated, confirming that this was a biologically effective intervention; for example, the prevalence of severe stunting (i.e., >3 SD below the reference median) was reduced from ~45 to 20% in Atole villages but remained about the level of 45% in Fresco villages throughout the study.

These and other effects described (e.g., birthweight, infant mortality) are important from a public health point of view. At the same time, the limited nature of both the intervention and its effects must be recognized. The nutrition intervention was unable to improve the diets to a point where children met their nutritional needs and hence the effects observed can never be taken as a measure of the full potential of nutrition interventions. Although the Atole contributed significant amounts of many nutrients (e.g., protein, thiamin, riboflavin, niacin, vitamin A, etc.), it contributed very little of some other nutrients as Allen (1995) points out: "Notably, neither supplement contributed much zinc, which may be growth limiting in the population, or ascorbic acid, which might have improved iron absorption and subsequently growth, or vitamin B-6, which might have improved cognitive development." Energy needs, as suggested earlier, may not have been met fully in children consuming Atole.

Another important aspect is that the infectious load was not diminished except through vaccinations. Although a medical care program was provided, programs in environmental and personal hygiene were not carried out. Diarrheal diseases, therefore, remained common in Atole and Fresco villages, most likely limiting the utilization of the dietary improvements and reducing the magnitude of the effects observed.

It is no surprise, therefore, that despite important improvements in physical growth, the children born to mothers exposed to Atole and themselves exposed to Atole for the first 3 y of life, still exhibited a substantial degree of growth retardation. Children in Atole villages grew 2.5 cm more than children in Fresco villages and the latter, whether because of the small nutritional contributions of the Fresco and/or because of the medical care program, grew 0.5 cm more relative to baseline values. Thus, the total effect of Atole on growth may have been ~3 cm of length at 3 y of age. However, children measured during the baseline were ~12 cm shorter than reference children, meaning that the intervention erased only 25% of the original growth deficit observed at 3 y of age.

Other than unintended effects of the INCAP presence, there were no elements designed to foster psychological development other than through the nutrition intervention, as made explicit in the principal hypothesis. For this reason, many researchers have not been surprised by the small magnitude of the effects on mental development observed in the preschool children.

Although it did not meet the full nutritional needs of the children, the INCAP intervention was conducted carefully and its design permits one to document that important effects occurred on infant mortality, birthweight and postnatal physical growth. Programs that include more than just supplementation, such as actions to bring about better feeding and child care practices together with improvements in environmental sanitation, personal hygiene and infectious diseases, among others, if properly implemented and effective, should achieve more. In retrospect, the INCAP longitudinal study demonstrates the power of nutrition interventions in that so much was achieved by so little.

The INCAP longitudinal study provides strong justification for focusing nutrition interventions on mothers and young children. Growth retardation in Guatemala, as is the case in other areas as well (Allen, 1995), is largely confined to the first 3 or even just the first 2 y of life. Why then, spend resources monitoring the growth of children 3–5 y of age, as many programs do, when the real concern should be with younger children? The results about the differential effects of the supplementation by age are clear; supplementation had a demonstrable impact on growth in the first 2 or 3 y of life but not from 3–7 y. This also may be taken as an argument for targeting scarce resources to very young children.

The follow-up study showed that the effects on height remained at adolescence and adulthood, although attenuated. The differences observed between Atole and Fresco subjects in the follow-up were small, 1.2 cm in males and 2.0 cm in females. Still, the prevalence of short maternal stature was reduced significantly in Atole compared with Fresco villages. Using the commonly accepted cut-off point of <149 cm as a measure of obstetric risk, we find that 34% of women were very short in Atole villages compared with 49% in Fresco women (Martorell, 1993). Few women in the United States would be this short; for example, the 5th percentile in young women in the United States is 152 cm according to Frisancho (1990). The effects on fat-free mass were also greater for women than for men, 2.0 and 0.8 kg, respectively. These differences between women in Atole and Fresco villages are important, equivalent to ~0.5 SD units. Such improvements in body size and composition are likely to lead to improved reproductive outcomes, a subject under investigation in the villages.

Maturation during adolescence, whether measured in terms of skeletal maturation or age at menarche, was not significantly affected by the intervention. On the other hand, age at menarche was found to be associated with socioeconomic status and a downward trend through time was observed. These findings suggest that maturation is under environmental influence, possibly of a nutritional nature. However, we were unable to confirm the latter. Planners and policy makers who might be concerned by possible effects of nutrition interventions in early childhood on the timing of puberty will be reassured by our findings. Ongoing research is assessing possible effects of the intervention on fertility milestones (e.g., age at marriage or union, age at first birth) and should address more fully the demographic implications of the nutrition intervention.

Another important effect, this time more apparent in men than in women, was on work capacity. The effect on maximal oxygen consumption, viewed in terms of standard deviation units, was large, equivalent to 0.7 SD. Differences between Atole and Fresco males remained significant even after controlling for fat-free mass, suggesting qualitative differences in tissue composition and function. One would expect from the literature that improvements in work capacity would result in increased productivity and incomes. However, Chung (1992) failed to demonstrate that work capacity resulted in higher wages. Several design and methodological problems may account for this. Also, few of the subjects were wage earners and instead most contributed labor to family agricultural activities; lack of adequate data on the labor inputs made by individuals and poor measures of household production made inclusion of nonwage earners difficult and resulted in small sample sizes. One problem was the young age of the subjects, many of them unmarried adolescents and young men when the data were collected in 1988–89 (the range in age was 11–26 y). Thus, better data on economic productivity collected when the sample settles into more permanent occupations and jobs a few years from now are needed to test the hypothesis that improvements in work capacity led to increased incomes.

The findings on intellectual development are surprising as noted earlier because of the larger magnitude observed in adolescence than in childhood. Using a composite variable (i.e., a factor score combining literacy, numeracy, general knowledge, Raven's Progressive Matrices, reading and vocabulary), the Atole-Fresco differences can be estimated as ~0.6 SD (compared with <0.2 SD in the preschool period). However, it is not the main effects but the interactions that should be emphasized; to repeat, these indicate that the nutrition intervention attenuated the negative relationship between socioeconomic status and performance and that it increased the educational returns to schooling. Schooling and intellectual capital, according to the literature, results in improved wages. Alba (1992), facing the same methodological difficulties described above, was nonetheless able to confirm that this was also the case for the study sample of wage earners. The additional rate of return to an additional year in school was found to be ~6%; weaker relationships were found when skills, such as vocabulary and numeracy, were used as measures of educational capital instead of years of school. Again, this and other questions concerning productivity and incomes are best addressed through better data collection.

In summary, the follow-up study has shown that nutrition interventions in pregnancy and early childhood culminate in the adolescent and adult in improvements in body size and composition and in intellectual performance. We were unable to link these improvements convincingly to economic productivity largely because of methodological reasons, but expect that these may be discerned later with better data. This means that advocates of nutrition programs aimed at mothers and children have an additional argument for them, namely that they improve the physical and intellectual endowment of adults. They also may refer to the reasonable but yet unproven hypothesis that these improvements in human capital will result in enhanced economic productivity. No doubt future extensions of our studies will provide a more comprehensive assessment of the value of nutrition programs for mothers and young children. Enough is known, however, to give these actions the highest priority, no matter how poor or rich the country may be.

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