Maternal and Child Nutritional Supplementation Are Inversely Associated with Fasting Plasma Glucose Concentration in Young Guatemalan Adults[1,2]

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ABSTRACT Cardiovascular disease and diabetes may be programmed early in life by abnormal development associated with undernutrition. We investigated whether maternal nutritional status (MNS; height, pregnancy weight gain, nonpregnant BMI, and prenatal supplementation) or childhood nutritional status (CNS; birth weight, length, ponderal index, height-for-age *Z*-score at 24 mo, and supplementation from 0 to 24 mo) were related to fasting plasma glucose levels in rural-born Guatemalan adults. We studied 209 men and 220 women (mean age 24.4 y) who were involved in a randomized trial of nutritional supplementation of their mothers during pregnancy and during their early childhoods, conducted from 1969 to 1977. In 2 villages, residents were offered Atole (3.8 MJ and 64 g protein/L); 2 other villages were offered Fresco (1.4 MJ/L, no protein). No associations were observed between anthropometric measures of MNS or CNS and fasting plasma glucose levels. In subgroup analyses, inverse associations (all $P < 0.15$) with birth size were found among women born to fatter mothers, women with low supplement intake, men born to short mothers, and men more severely stunted at 24 mo. Prenatal supplementation was inversely associated with fasting plasma glucose among women [-0.40 ± 0.17 mmol/(L · MJ · d), $P = 0.02$]. Among men, postnatal intake of supplementation of 0.10 to 0.20 MJ/d was associated with up to a 0.56 mmol/L reduction in fasting plasma glucose ($P = 0.03$), but intake in excess of 0.20 MJ/d provided no added benefit. Among women, the benefit of postnatal supplementation was restricted to those born thin (test for interaction $P = 0.10$). Improving the nutritional status of undernourished women and children may have positive long-term consequences. J. Nutr. 134: 890–897, 2004.

KEY WORDS: • *glucose* • *Guatemala* • *birth weight* • *supplementation*

It is hypothesized that adult metabolic disease originates early in life through adaptations made under conditions of a poor nutritional environment (1). Most of the literature uses birth size as a proxy for prenatal nutrition. An inverse association between birth size and various determinants or consequences of type-2 diabetes mellitus (2–4) and cardiovascular disease (5–8) is often observed.

Growth in childhood may modulate the propensity for adult disease. Rapid growth, particularly among those born small, may exert a harmful effect (8). The evidence to date is mixed, with some studies reporting positive associations (9–13), and others reporting inverse (12,14,15) or no associations (16) between childhood growth and various risk factors for adult metabolic disease. In developing countries where stunting is prevalent, catch-up growth is related to increased short-term survival (17). The long-term consequences of catch-up growth on adult chronic disease need further clarification, as the results to date differ between genders, and are dependent on the specific parameter of growth (e.g., height, weight, BMI) and age measured.

Few studies of adult offspring have managed to examine maternal nutritional status. Maternal diet influences fetal growth (18), but robust evidence to support the benefit of nutritional intervention during pregnancy in relation to fetal programming is currently lacking. Maternal height, weight, and body composition may affect the ability to deliver nutrients for optimal fetal growth and development (19,20). Most

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studies (21–26), but not all (27–29), report that better maternal nutritional status is associated with reduced risk of adult metabolic disease among offspring.

A follow-up study on young adults, who were born during a longitudinal nutritional supplementation trial in rural Guatemala, presents a unique opportunity to investigate the effects of birth size, childhood growth, and maternal nutritional status on adult glucose metabolism, and to compare the effects of two different dietary supplements consumed by the mother during pregnancy and by the mother and the offspring in early childhood (Fig. 1). We hypothesized that poor nutritional status of the mother or of the infant would be associated with elevated fasting plasma glucose levels, and that subsequent enhanced nutritional supplementation would ameliorate these adverse effects.

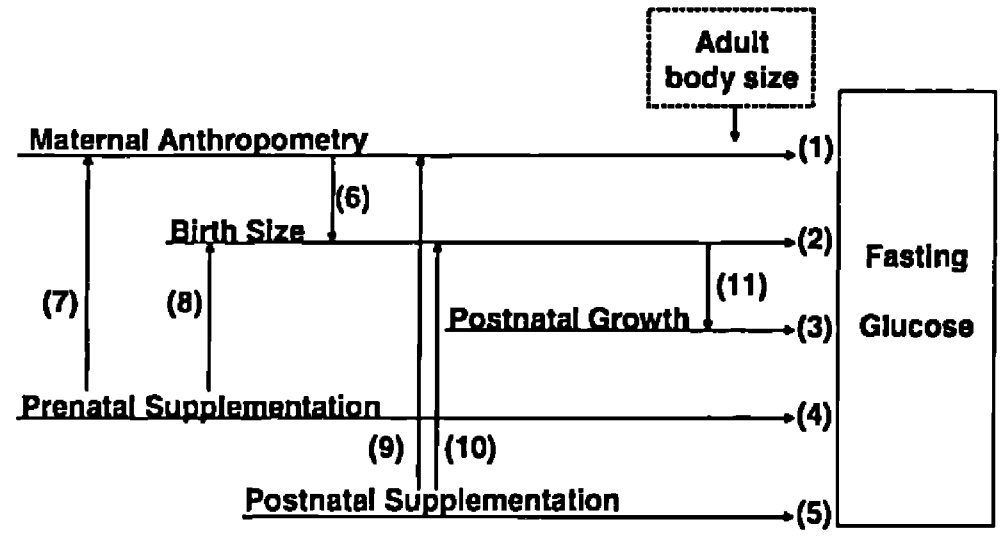

FIGURE 1 Proposed relationships between maternal and child nutritional status and adult fasting glucose (FG) concentration in plasma. *Hypotheses 1- 3*: Poor MNS (indicated by anthropometry), smaller birth size, and childhood stunting is associated with elevated FG. *Hypotheses 4 and 5*: Pre- and postnatal supplementation is associated with lower FG. *Hypothesis 6*: Small birth size and poor MNS synergistically elevate FG. *Hypotheses 7 and 8*: Prenatal supplementation ameliorates the adverse effect of poor MNS or small birth size on FG. *Hypotheses 9 and 10*: Postnatal supplementation ameliorates the adverse effect of poor MNS or small birth size on FG. *Hypothesis 11*: Childhood growth ameliorates the adverse effect of small birth size on FG. There is an ongoing debate whether adult body size acts as a mediating variable in these relationships. Therefore, the hypotheses were examined with and without adult body size in the model.

SUBJECTS AND METHODS

Study population, field surveys, and data collection. *1969–1977 INCAP Longitudinal Study.* Individuals interviewed for the present study were participants in a longitudinal study on growth and development conducted between 1969 and 1977 by the Instituto de Nutrición de Centro América y Panamá (INCAP)[4] in 4 villages of mixed Spanish-Mayan descent, located 40 to 110 km east of Guatemala City, Guatemala. Village residents were provided with improved medical care and either Atole, a dietary supplement providing protein, micronutrients and 3.80 MJ (900 kcal)/L, or Fresco, which provided only micronutrients and 1.35 MJ (330 kcal)/L. The supplements were distributed and consumed twice daily in a centrally located feeding hall in each village. The supplement types were assigned at random, with the village as the unit of randomization.

Data collection. Supplement intake to the nearest 10 mL was recorded for all pregnant and lactating women and their offspring up to age 7 y. Height and weight of the mothers and children was recorded at select intervals, including birth. Birth length was measured 7 to 14 d following birth. Detailed descriptions of the original study and subsequent follow-up surveys appear elsewhere (30,31).

1997–1998 Follow-up study. Participants eligible for follow-up were born between 1969 and 1977, had a recorded birth weight, and had a history of at least 1 y of growth monitoring in childhood. Participants also had to reside, or be available for interview, in one of the original study villages or in Guatemala City. Of the eligible cohort members who could be traced, 473 (78%) were examined (237 men and 236 women). Reasons for nonexamination included not being at home on multiple visits ($n = 36$), serious handicaps or chronic illness not related to glucose metabolism ($n = 4$), pregnancy or nursing a baby <6 mo old ($n = 25$), and refusal to participate in the study ($n = 70$). Institutional review boards at INCAP and Emory University approved the study protocol, and all participants provided written consent.

Data collection. Participants were instructed to fast overnight. The duration of fasting was calculated by subtracting the most recent time of food or drink consumption from the time of the morning blood analysis. Blood was obtained by fingerprick. Plasma glucose level was assayed by a glucose oxidase reaction, using the Cholestech LDX System (32). Standardized anthropometry was used to measure height, weight, and natural waist (smallest) and hip circumference. The BMI and waist-to-hip ratio (WHR) were calculated. Diet (33), customary physical activity level (34), and other relevant covariates were ascertained by interview. The current place of residence was characterized as rural or urban. Complete details about the methods of data collection from the 1997–1998 study are available elsewhere (35–37).

Variable definitions. Prenatal supplement intake was calculated as the mean daily energy intake from the supplement by the mother from the time pregnancy was identified to birth. Postnatal supplement intake was calculated as the mean daily energy intake from the supplement from birth to age 24 mo. The supplement type was either Atole or Fresco.

Maternal nutritional status (MNS) was characterized by maternal height, pregnancy weight gain, or nonpregnant BMI. Pregnancy weight gain was calculated as the average monthly weight gain from mo 4 to birth. Nonpregnant BMI was calculated using maternal weight ≥ 5.5 mo postpartum.

Childhood nutritional status (CNS) indicators included birth size (weight, length, and ponderal index) and postnatal stature [height-for-age Z-score (HAZ)]. The ponderal index was calculated as weight/length^3 (kg/m^3). The HAZ at 24 mo was calculated using the 2000 National Center for Health Statistics growth charts. Previous analysis of the participants of the INCAP Longitudinal Study showed that HAZ stabilized at ~12 mo of age (38). Therefore, if height was not measured at 24 mo, we interpolated a 24-mo HAZ using the two nearest measurements within 1 y above and below 24 mo, with the assumption that HAZ remained relatively constant after 12 mo. If surrounding measurements within 1 y were not available, HAZ was set to missing.

Exclusions and missing data. We excluded from analysis participants who did not have a plasma glucose measurement (men, $n = 20$; women, $n = 8$) or who had not fasted for at least 8 h prior to blood drawing (men, $n = 8$; women, $n = 8$). Men and women were each missing 8% of the independent variable data. Missing data were imputed using a multiple imputation method (39). Specifically, we imputed missing values for continuous variables using a mean plus random noise approach (i.e., imputed value = mean + SD × seed, where the seed is a value generated from the standard normal distribution, with a mean of 0 and a variance of 1), constrained to fall within the range of the observed data for each variable. No categorical variables required imputation. We repeated this procedure to create 15 unique datasets. The 15 datasets were analyzed independently, then the parameter estimates and standard errors were com-

[4] Abbreviations used: CNS, child nutritional status; HAZ, height-for-age *Z*-score; INCAP, Instituto de Nutrición de Centro América y Panamá; MNS, maternal nutritional status; WHR, waist-to-hip ratio.

bined by using the SAS procedure MIANALYZE. The final population for analysis consisted of 209 men and 220 women.

Statistical methods. Data for men and women were analyzed separately using SAS (version 8; SAS Institute). We tested main effect associations between adult fasting plasma glucose level and MNS or CNS, supplementation quantity, and supplement type. We also tested interactive associations of MNS or CNS or supplementation quantity with supplement type; MNS with birth size; birth size with postnatal growth; and birth size or MNS with supplementation quantity (Fig. 1).

All models were adjusted for socioeconomic status at birth, gestational age, and a set of covariates previously shown to explain maximum variance in fasting plasma glucose levels among the study population (35): village size, supplement type, current age, energy intake, physical activity level (women only), and migration status (women only). There is an ongoing debate as to the appropriateness of adjusting associations between MNS and CNS and adult disease for adult body size, because adult body size is potentially a mediating variable (40). Models were also analyzed with additional adjustment for adult body size [BMI, WHR, and BMI × WHR (men only)]. Results from these models proved similar, so all results are provided without adjustment for adult body size.

Among models where supplementation quantity was the exposure variable of interest, we included both prenatal energy intake by the mother and postnatal energy intake by the child to separate the potential associations derived from different sources of supplementation. Atole and Fresco differed in energy concentration per unit volume, but contained micronutrients at a constant concentration by volume. We examined the main effects of energy or volume intake and interactions between supplement types by supplement quantity (energy or volume) to facilitate clarification of the separate roles of protein, energy, and micronutrients.

Approximately 25% of the subjects were same-sex siblings, resulting in correlated data. Failure to control for correlated data could lead to incorrect inferences (41,42). Therefore, we used a generalized estimating equations approach (implemented in the SAS procedure GENMOD), with an exchangeable working matrix. Empirically adjusted standard errors were used for inference. Main effects were considered significant at $P < 0.05$ and interaction terms at $P < 0.15$.

RESULTS

Mothers of the study participants were short (Table 1); 12% of the mothers were underweight (BMI $\leq$ 18.5 kg/m^2), and 14% had a BMI $\geq$ 25 kg/m^2; of these, 3 had a BMI $\geq$ 30 kg/m^2. At birth, 6% of men and women weighed <2500 g, and 67% were stunted by 24 mo of age (HAZ < -2.0). At the CVD follow-up study, the age of our cohort ranged from 20 to 29 y. We identified 1 woman with diabetes (fasting plasma glucose $\geq$ 7.0 mmol/L), and 6 men and 4 women with impaired fasting plasma glucose (6.1 mmol/L $\leq$ fasting plasma glucose > 7.0 mmol/L). The BMI of 10% of men and 20% of women was in the range from 25 to 29.99 kg/m^2; 1% of men and 9% of women had a BMI $\geq$ 30 kg/m^2; and 24% of men and 20% of women had central obesity (men. WHR > 0.90; women, WHR >0.85). Height at age 24 mo, reported as a Z-score, was strongly related to adult attained height (men, $r = 0.67$; women, $r = 0.59$; $P < 0.0001$ for both).

Men excluded from the analysis had a lower socioeconomic factor score at birth (-0.46 ± 0.66, $P = 0.01$) compared to the analytic population. Among women, only mean home dietary energy intake at the time of the CVD study was higher among those excluded (11.4 ± 2.1 MJ/d, $P = 0.04$).

Maternal anthropometry, birth size, and postnatal growth. The direction of the main effect associations between adult fasting plasma glucose level and indicators of birth size, postnatal growth, or MNS generally differed between genders. However, all β-values were small, and none of the associations were significant. There were no significant interactions with supplement type.

Prenatal and postnatal supplementation. Among men, supplement type had no main effect (Table 2). Among women, exposure to Atole was associated with a 0.29-mmol/L (SE 0.13, $P = 0.03$) lower adult fasting plasma glucose level compared to those exposed to Fresco. However, this association was not significant after adjusting for adult body size, due to an increase in the standard error ($\beta = -0.30$ mmol/L in the Atole villages, SE 0.16, $P = 0.07$).

In models examining associations of energy intake from supplementation, the sample size was reduced to 154 and 167 for men and women, respectively, due to censoring at the termination of the study that left incomplete data on 2 y of postnatal supplementation. Men and women who were excluded from these analyses were a mean of 4 y younger, were larger at birth, were thinner, consumed less energy as adults, and had lower physical activity levels.

Among men, prenatal energy supplementation was not associated with adult fasting plasma glucose level. Among women, prenatal energy intake from the supplement was associated with a decrease of 0.39 ± 0.16 mmol/(L · MJ · d) in adult fasting plasma glucose level ($P = 0.02$). There was no evidence of a nonlinear relationship. The volume of prenatal supplementation was inversely associated with fasting plasma glucose ($\beta = -0.87 \pm 0.42$ mmol/L per L/d of supplement, $P = 0.04$).There were no interactions between supplement type and either prenatal energy supplementation or volume of prenatal supplementation affecting fasting plasma glucose level in either men or women.

Among men, there was a significant ($P = 0.02$) inverse logarithmic association between postnatal energy intake from the supplement and fasting plasma glucose level. This model found no interaction with supplement type, which suggests a steep reduction in adult fasting plasma glucose concentration with postnatal energy intake up to ~0.10 to 0.20 MJ/d, with no added benefit above this level. There was a linear inverse association between the volume of postnatal supplementation and fasting plasma glucose level ($\beta = -1.5 \pm 0.49$ mmol/L per L/d of supplement, $P = 0.002$) as well as an interaction between volume of postnatal supplementation and supplement type ($P = 0.11$).

Among women, postnatal energy intake had no linear main effect on adult fasting plasma glucose level. The interaction between postnatal energy intake from supplement and supplement type was significant ($P = 0.14$). Although the regression slopes differed between the Atole [$\beta = 0.32 \pm 0.21$ mmol/(L · MJ · d), $P = 0.13$] and Fresco [$\beta = -3.0 \pm 2.2$ mmol/(L · MJ · d), $P = 0.17$] groups, neither differed significantly from 0, and the interaction was not significant after adjustment for adult body size. There was no evidence of a nonlinear relationship between postnatal energy intake and fasting plasma glucose level in women. There was a linear interaction between the volume of postnatal supplementation and the fasting plasma glucose level ($P = 0.13$).

Maternal anthropometry and birth size. There were two interactions between maternal anthropometry and birth size. Among men, the association between birth length and adult fasting plasma glucose level was modified by maternal height (interaction $P = 0.08$). Among men born to the shortest mothers, birth length was inversely related to adult fasting

TABLE 1

Characteristics of the Guatemalan men and women included in the analyses[1]

Characteristic	Men		Women	
	n		*n*	
Maternal and early childhood[2]				
Maternal height, *cm*	199	149.5 ± 5.3	210	149.6 ± 5.2
Average pregnancy weight gain,[3] *kg/mo*	123	1.4 ± 0.6	128	1.5 ± 0.7
Postpartum BMI, *kg/m²*	143	21.7 ± 2.9	157	21.5 ± 2.8
Energy intake from supplement during pregnancy, *MJ/d*	209	0.42 ± 0.38	220	0.40 ± 0.33
Supplement type, *% Atole*	209	54	220	50
Birth weight, *kg*	209	3.13 ± 0.51	220	3.05 ± 0.43
Birth length, *cm*	174	50.5 ± 2.3	185	49.6 ± 2.1
Ponderal index, *g/cm³*	174	2.4 ± 0.4	185	2.5 ± 0.3
Gestational age, *wk*	154	39.9 ± 2.3	169	39.7 ± 2.8
HAZ at 24 mo	179	−2.3 ± 1.0	189	−2.3 ± 1.0
Energy intake from supplement from birth to 2 y, *MJ/d*	154	0.29 ± 0.36	167	0.23 ± 0.28
Socioeconomic factor score at birth	199	−0.10 ± 0.94	209	−0.13 ± 0.86
Adult[4]				
Plasma glucose, *mmol/L*	209	4.8 ± 0.6	220	4.7 ± 0.8
Age, *y*	209	24.5 ± 2.4	220	24.3 ± 2.2
BMI, *kg/m²*	208	22.1 ± 2.4	218	23.6 ± 4.2
WHR	208	0.87 ± 0.04	217	0.81 ± 0.05
Home dietary energy intake, *MJ/d*	190	14.0 ± 3.6	213	10.1 ± 2.4
Physical activity level, *Metabolic Equivalency Units/d*	209	1.63 ± 0.27	220	1.52 ± 0.10
Residence, *% urban*	209	33	220	19

[1] Values are means ± SD for continuous variables and percentage of subjects for categorical variables. The *n*-values represent the sample size for each variable; 429 subjects (209 men, 220 women) were included in the analysis. All subjects who fasted at least 8 h were included in the analysis.
[2] Characteristics were measured during the 1969–1977 study.
[3] Pregnancy weight gain was calculated as the mean weight gain per month from mo 4 to birth.
[4] Characteristics were measured during the 1997–1998 study.

plasma glucose level. As maternal height increased, this inverse association was attenuated, and became positive among men born to the tallest mothers. Among women, the association between ponderal index and adult fasting plasma glucose level was modified by maternal BMI (interaction $P < 0.15$). The larger the mother, the more strongly the child's ponderal index related inversely to adult fasting plasma glucose level. There was a similar pattern with birth weight, but the interaction term was not significant ($P = 0.21$).

Maternal anthropometry, birth size and prenatal supplementation. There were no interactions between maternal anthropometry and prenatal energy intake from the supplement in either men or women. Among men, there was an interaction between birth weight and prenatal energy intake from the supplement ($P = 0.05$), with a positive association between birth weight and adult fasting plasma glucose level in men whose mothers consumed <0.42 MJ/d (the median intake) from the supplement during pregnancy and an inverse

TABLE 2

Adjusted multiple imputation parameter estimates for the main effects of supplementation on adult fasting plasma glucose concentration in young Guatemalan men and women[1]

Variable	Men	Women
	β, mmol/L	
Supplement type, *Atole = 1; Fresco = 0*	−0.024 ± 0.078	−0.29 ± 0.13†
Prenatal supplement, *MJ/d*	0.033 ± 0.12	−0.39 ± 0.16†
Postnatal supplement,[2] *MJ/d*	0.0021 ± 0.0011*	0.28 ± 0.21
Postnatal supplement × supplement type	—	3.4 ± 2.3*
Postnatal supplement, *MJ/d*	—	−3.0 ± 2.2
Supplement type, *Atole = 1; Fresco = 0*	—	−0.55 ± 0.29*

[1] Values represent change in fasting plasma glucose concentration ($\beta \pm$ SE) per unit of the exposure variable); $n = 154$ for men, $n = 167$ for women; * $P < 0.15$, † $P < 0.05$. Each exposure variable and interaction was tested in a separate model. Models were adjusted for gestational age, socioeconomic status, village size, adult age, energy intake, physical activity (women only), and migration status (women only). Analyses of exposures other than supplement type were also controlled for supplement type.
[2] Among men, there was an inverse logarithmic relationship between postnatal supplementation and fasting plasma glucose concentration. The postnatal supplementation variable was transformed [1/(MJ · d)] prior to regression.

association. in those whose mothers consumed >0.62 MJ/d (the 75th percentile). The significance of this interaction, however, was dependent on the inclusion of one influential observation, a man with a birth weight of 5.5 kg.

In contrast, among women there was an inverse association between birth weight and adult fasting plasma glucose level only in those whose mothers consumed less energy (<0.37 MJ/d) from the supplement during pregnancy (Fig. 2). As maternal energy intake from supplement increased, the association between birth weight and adult plasma glucose was attenuated, and then became positive at the highest maternal energy intakes ($P = 0.12$). The association between prenatal intake from supplement and adult plasma glucose level was attenuated as birth weight increased, with little effect of prenatal energy supplementation in those with higher birth weights. There was a similar association with ponderal index (interaction $P = 0.08$).

Maternal anthropometry, birth size, and postnatal supplementation. There were no interactions between maternal anthropometry and postnatal energy intake from the supplement in either men or women. Birth size modified the association between postnatal supplementation and fasting plasma glucose level in men and women (Fig. 3). Among men, the inverse relationship between postnatal supplementation and fasting plasma glucose level was attenuated as birth weight increased ($P = 0.02$). Among women, the association became positive as birth weight increased ($P = 0.11$). There was a similar relationship with the ponderal index in women.

Birth size and postnatal growth. Birth weight modified the association between postnatal growth and adult fasting plasma glucose level in men (interaction $P = 0.008$). Among men born small, there was an inverse association between HAZ at 24 mo and adult fasting plasma glucose, whereas the association was positive among men with the highest birth weights (Fig. 4). There was relatively no association between childhood stature and adult fasting plasma glucose level in those with intermediate birth weights. There were no interactions between birth size and postnatal growth in women.

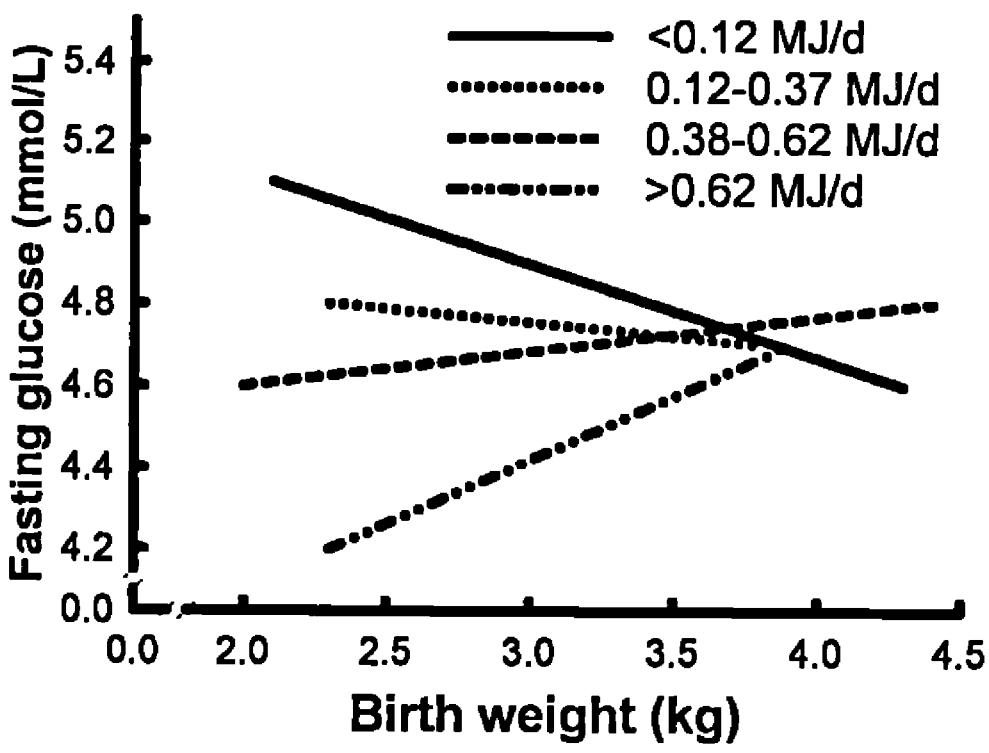

FIGURE 2 Prenatal energy supplementation from the time pregnancy was identified to birth modifies the relationship between birth weight and adult fasting plasma glucose concentration among Guatemalan women born during the INCAP supplementation study (1969–1975) and examined in 1997–1998. Data for individuals who did not receive 2 y of postnatal supplementation were censored. The model was adjusted for village size, socioeconomic status, gestational age, postnatal energy intake and supplement type, adult age, home dietary energy intake, physical activity, and migration status, then solved using mean covariate values within each prenatal energy intake quartile. The figure represents the range of the data.

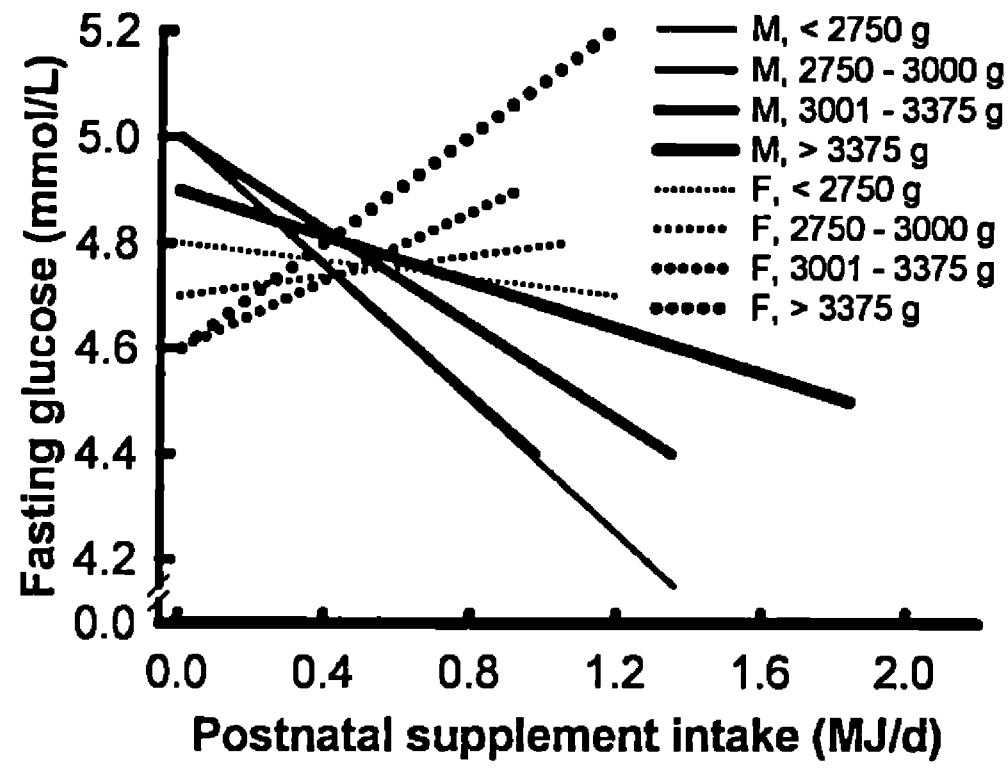

FIGURE 3 Energy supplementation from birth to 24 mo modifies the relationship between birth weight and adult fasting plasma glucose concentration among Guatemalan men and women born during the INCAP supplementation study (1969–1975) and examined in 1997–1998. Data for individuals who did not receive 2 y of postnatal supplementation were censored. The model was adjusted for village size, socioeconomic status, gestational age, prenatal energy intake and supplement type, adult age, home dietary energy intake, physical activity, and migration status (women only), then solved using mean covariate values within each postnatal energy intake quartile. The figure represents the range of the data. Solid lines denote men, dotted lines denote women. Increasing thickness of lines corresponds to increases in birth weight.

DISCUSSION

We examined the relation between several indicators of MNS and CNS and adult fasting plasma glucose level in young Guatemalan men and women. We found few consistent relations between anthropometric indicators of MNS or CNS and adult fasting plasma glucose (hypotheses 1–3, 6, and 11, Fig. 1). However, we observed a pattern of reduced adult fasting plasma glucose with improved nutrition from supplementation early in life (hypotheses 4 and 5), particularly among those born small (hypotheses 8 and 9). Supplementation did not modify the relation between MNS and fasting plasma glucose (hypotheses 7 and 10). Our finding that supplementation is independent of birth size adds to the body of evidence that maternal nutrition plays a role in adult health even without an effect on birth size (43,44).

Prenatal supplementation has beneficial effects, independent of birth size, on multiple outcome parameters. Among the multiple tests in our analysis, we found either a beneficial or null effect of prenatal supplementation, with one exception. We found this adverse effect in only one gender and with only one measure of birth size, and it may represent a chance

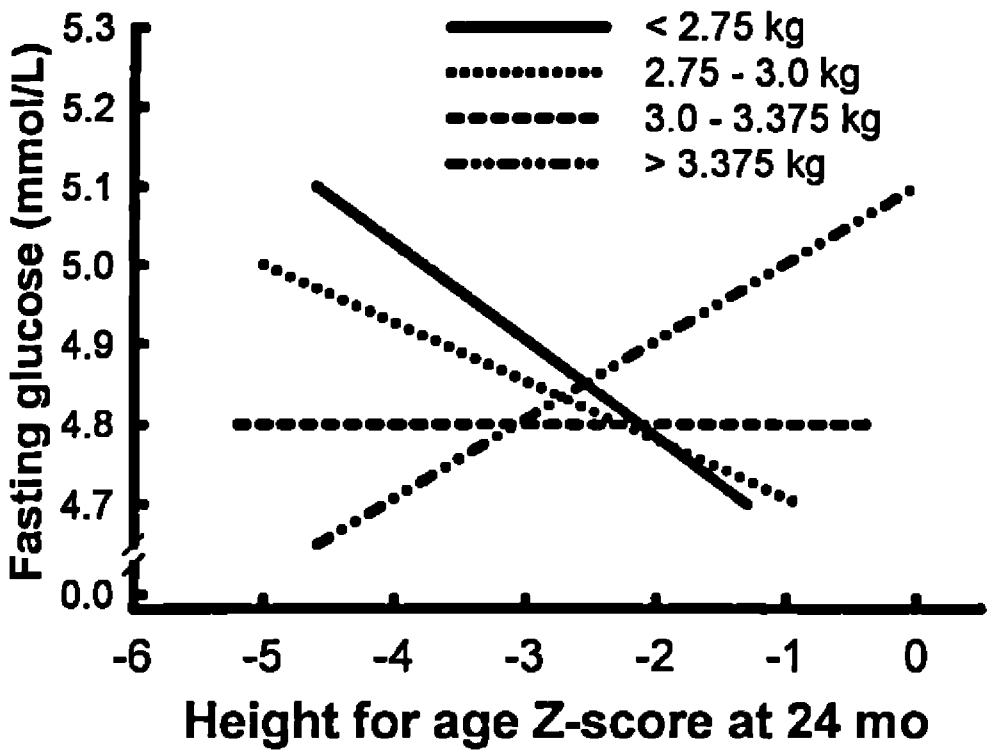

FIGURE 4 Birth weight modifies the relationship between childhood stature at 24 mo and adult fasting plasma glucose concentration among Guatemalan men born during the INCAP supplementation study (1969–1975) and examined in 1997–1998. Data for individuals who did not receive 2 y of postnatal supplementation were censored. The model was adjusted for village size, socioeconomic status, gestational age, supplement type, adult age, and home dietary energy intake, then solved using mean covariate values within each postnatal energy intake quartile. The figure represents the range of the data.

observation. Our findings thus suggest little risk of adverse effects from supplementation of chronically undernourished pregnant women and young children with respect to plasma glucose levels later in life.

Postnatal supplementation was associated with reduced adult plasma glucose concentration. The inverse logarithmic association among men suggests that only small amounts of supplemental energy (0.10 to 0.20 MJ/d) are needed to achieve maximum benefit in adult plasma glucose level reduction. Among women, the benefit of postnatal supplementation was limited to those born thin. Postnatal supplementation was positively associated with plasma glucose levels in women who weighed more at birth, suggesting adverse effects of overnutrition in women who were better nourished at birth. Our findings support the general recommendation of supplementation in early childhood for undernourished children. Analyses of the energy content and volume of postnatal supplementation suggests that energy, protein, and micronutrients play a role in the reduction of fasting plasma glucose levels in men, whereas protein appears to be important in women.

Maternal height and body composition are markers of metabolic capacity to provide nutrients to the fetus (19). Mothers in our study were stunted, presumably due to chronic malnutrition, but not necessarily thin. In China, low maternal BMI late in pregnancy, but not pregnancy weight gain, was associated with reduced glucose tolerance, suggesting that low maternal BMI around conception may predispose offspring to glucose intolerance (21). In Pune, India, children born to shorter mothers were more insulin resistant that those born to taller mothers (45). We found no associations with maternal height, postpartum BMI, or mean monthly weight gain during trimesters 2 and 3. These differences may be due to the fact that the mothers in our study were participating in a supplementation trial. The additional nutrition may have attenuated any fetal programming attributable to MNS. We also used BMI measured at least 6 mo postpartum as a proxy measure for nonpregnant BMI. Finally, maternal BMI and pregnancy weight gain accounted for a third of all our missing data, making associations with these variables the least reliable of all our putative determinants.

Previous studies showing an inverse relationship between birth size and indicators of glucose tolerance were primarily conducted among Caucasian populations in developed countries (3,4,6,9,46–51). Studies of individuals from developing countries, where chronic undernutrition is more common, yielded more mixed results (16,21,45,52–54). The lack of consistent associations in developing countries may relate to the absence of other adult lifestyle risk factors associated with urbanization and the nutritional transition. The majority of our study population still resided in rural villages, and the prevalence of these risk factors was still lower than in most industrialized nations. Genetic differences may also play a role (55,56).

Our study was conducted in the context of a supplementation trial aimed at improving childhood growth and development. Although supplementation with Atole increased the length of 3-y-old children by 2.5 cm and reduced prevalence of severe stunting (HAZ < 3) by half (57), chronic undernutrition remained common, and the children remained stunted compared to reference standards. In Pune, India, children born small who were taller at age 8 y were more insulin resistant (45). In contrast, our data suggest a benefit of catch-up growth from birth to age 24 mo due to improved nutrition through supplementation, insofar as poor growth in utero followed by better growth in childhood was associated with reduced adult plasma glucose concentration.

Interestingly, almost all associations tested were opposite in direction between men and women. Women were more sensitive to improved prenatal nutrition, whereas men were more sensitive to improved postnatal nutrition. Gender differences have been reported elsewhere (23,46) and may be related to differential growth patterns or endocrinologic differences (58).

Our study did have limitations. The unit of randomization was the village, but analysis was on an individual level, thus limiting the ability to infer causal associations. In addition, the extensive set of a priori associations among multiple indicators of MNS and CNS and intakes of supplement tested resulted in the examination of 120 interaction models, of which 21 were significant ($P < 0.15$). We cannot rule out chance as an explanation for all these significant interactions, and therefore strongly caution against inferring causality for these specific associations in the absence of replication in other data sets, especially where we observed inconsistent associations across similar measures and genders.

We used a multiple imputation method to retain individuals with missing data in the analyses. Imputation of variables was based on the distribution of the study population without regard to the outcome variable. Therefore, the estimates using imputed data are likely to be conservative, because estimates will be biased to the null if there is indeed a relationship.

Resource constraints and cultural barriers limited the measures of glucose homeostasis available, and capillary glucose is clearly a suboptimal measure of preclinical disease, especially given the young age of the study cohort. The ability to detect associations using this measure suggests that the findings would have been stronger using tests more predictive of glucose homeostasis.

In conclusion, we found little association between anthropometric measures of either maternal or childhood nutritional status and fasting glucose. However, consistent with the underlying premise postulated by the fetal origins hypothesis, improved prenatal nutrition through dietary supplementation during early life was associated with reduced fasting glucose levels in adulthood. The benefit of postnatal supplementation may be restricted to men and women born thin. This study illustrates another benefit of public health strategies and policies to improve the nutritional status of women and children.

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