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Effects of Infant Birthweight and Maternal Body Mass Index in Pregnancy on Components of the Insulin Resistance Syndrome in China

Jie Mi, PhD; Catherine Law, MD; Kong-Lai Zhang, MD; Clive Osmond, PhD; Claudia Stein, PhD; and David Barker, FRS

Background: Reduced birthweight is associated with increased risk for the insulin resistance syndrome. Part of this risk is hypothesized to originate from undernutrition in utero. The prevalence of the insulin resistance syndrome increases in countries that undergo the transition from chronic malnutrition to adequate nutrition, when postnatal nutrition improves more rapidly than prenatal nutrition.

Objective: To determine whether the components of the insulin resistance syndrome are associated with reduced fetal growth and maternal undernutrition.

Design: A nonconcurrent, prospective study of men and women whose mothers' heights and weights were recorded during pregnancy.

Setting: Beijing, China.

Participants: 627 men and women (mean age, 45 years) whose mothers' obstetric records were preserved.

Measurements: Adult offspring's blood pressure, plasma glucose levels, insulin levels, and lipid concentrations during an oral glucose tolerance test. The main explanatory measurements were mothers' body mass index during pregnancy and offspring's birthweight and adult size.

Results: After adjustment for sex and current body mass index, low birthweight was associated with elevated plasma glucose levels, insulin levels, triglyceride concentrations, and blood pressure. For every 1-kg increase in birthweight, systolic blood pressure decreased by 2.9 mm Hg (95% CI, 0.3 to 5.4 mm Hg) and the 2-hour plasma glucose level decreased by 5.1% (CI, 0.7% to 9.3%). Low maternal body mass index in early and late pregnancy was associated with elevated levels of plasma glucose, insulin, and triglycerides in adult offspring but was not associated with elevated blood pressure.

Conclusions: Risk for the insulin resistance syndrome may be partially established through low maternal body mass before pregnancy and consequent fetal undernutrition. This risk is independent of that associated with adult obesity. In developing countries such as China, improved nutrition in girls and young women may offer long-term benefits to offspring.

For author affiliations, current addresses, and contributions, see end of text.

The prevalence of type 2 diabetes mellitus and coronary heart disease increases as countries undergo a transition from chronic malnutrition to adequate nutrition (1–3). The insulin resistance syndrome, in which hyperinsulinemia, impaired glucose tolerance, elevated blood pressure, and elevated serum triglyceride concentrations occur together, is a precursor to these disorders (4). The prevalence of the syndrome increases with adult obesity (4).

In developed countries, reduced birthweight or thinness at birth is associated with increased risk for the insulin resistance syndrome and its various components (5–7). Because of this, some researchers hypothesize that part of the risk for the insulin resistance syndrome originates from the fetus' adaptations to intrauterine undernutrition (8).

We hypothesized that poor fetal nutrition (resulting from chronic maternal malnutrition) and increasing body mass index among adults may help explain the growing prevalence of the insulin resistance syndrome in developing countries. As part of this hypothesis, we expected that the associations of birthweight with the components of the insulin resistance syndrome in developing countries would be similar to those in developed countries and that measures of maternal undernutrition would be associated with higher levels of the components of the insulin resistance syndrome. To date, no published studies have been able to test this theory.

We studied men and women who were born in Beijing, China, approximately 45 years ago. At that time, much of China's population was chronically malnourished. According to detailed obstetric records, the mothers of the participants in our study were thin and stunted. The study participants lived through a period of nutritional transition, and al-

Table 1. Participants' Adult Measurements, Measurements at Birth, and Mothers' Measurements

| Variable* | Mean Value \pm SD | |
|---|---------------------|--------------------|
| | Men (n = 309) | Women (n = 318) |
| Adult measurements | | |
| Age, y (n = 627) | 45.1 \pm 1.4 | 45.2 \pm 1.3 |
| Height, cm (n = 627) | 172.5 \pm 6.1 | 160.5 \pm 5.3 |
| Weight, kg (n = 627) | 73.4 \pm 10.5 | 60.1 \pm 8.5 |
| Body mass index, kg/m ² (n = 627) | 24.7 \pm 3.1 | 23.3 \pm 3.1 |
| Systolic blood pressure, mm Hg (n = 627) | 128 \pm 13 | 121 \pm 17 |
| Diastolic blood pressure, mm Hg (n = 627) | 80 \pm 10 | 70 \pm 11 |
| Measurements at birth | | |
| Birthweight, g (n = 627) | 3196 \pm 438 | 3094 \pm 442 |
| Crown-to-heel length, cm (n = 626) | 49.7 \pm 2.0 | 49.1 \pm 1.9 |
| Ponderal index, kg/m ³ (n = 626) | 26.0 \pm 2.0 | 26.1 \pm 2.4 |
| Head circumference, cm (n = 623) | 32.1 \pm 1.4 | 31.7 \pm 1.4 |
| Placental weight, g (n = 608) | 524 \pm 102 | 518 \pm 93 |
| Length of gestation, wk (n = 611) | 39.8 \pm 2.0 | 40.1 \pm 2.0 |
| Mothers' measurements | | |
| Age, y (n = 627) | 28.3 \pm 5.0 | 28.2 \pm 5.4 |
| Height, cm (n = 591) | 155.3 \pm 6.0 | 155.9 \pm 5.9 |
| Weight at 15 weeks of pregnancy, kg (n = 232) | 50.2 \pm 6.2 | 50.8 \pm 6.1 |
| Weight at 38 weeks of pregnancy, kg (n = 599) | 60.1 \pm 6.7 | 60.2 \pm 6.2 |
| Body mass index at 15 weeks of pregnancy, kg/m ² (n = 226) | 20.8 \pm 2.6 | 21.0 \pm 2.6 |
| Body mass index at 38 weeks of pregnancy, kg/m ² (n = 584) | 24.9 \pm 2.5 | 24.7 \pm 2.3 |
| Systolic blood pressure at 38 weeks of pregnancy, mm Hg (n = 622) | 109 \pm 14 | 108 \pm 13 |

* n = number of measurements of obtained.

though they were relatively short in stature, their body mass indexes as adults approached those seen in adults in the United Kingdom (9).

Methods

Information on Mothers and Infants

The Peking Union Medical College Hospital in Beijing kept exceptionally detailed obstetric records that include each baby's size at birth and the duration of gestation (calculated from the date of the last menstrual period). Contemporary accounts indicate that during 1948 to 1954, the years in which the study participants were born, pregnant women who visited the hospital could be divided into two groups. Women in the first group could pay some of their medical bills and received antenatal and intrapartum care. Women in the second group were poor and were admitted close to the time of delivery.

Height, weight, and blood pressure were measured in some women during the first half of their pregnancies (5 to 20 weeks) and subsequently; in other women, these measurements were obtained only during late pregnancy. The mothers were measured an average of 7 times during pregnancy (range, 0 to 15 times). Medical records also contained information on the occupations of the participants' fathers, grouped into 10 categories. We

combined these data into 2 broader categories: "manual" and "nonmanual."

Tracing and Collecting Information on Adult Offspring

Authorities at the Peking Union Medical College Hospital allowed us to examine the obstetric records of 1921 women who had sequential, singleton live births in the hospital from July 1948 to December 1954. We sent their identification data to the Beijing Municipal Residential Record Office and found that 885 of the women were living in Beijing. We visited each of them, and they told us the current address of their now-middle-aged sons or daughters. The 725 offspring whom we traced in this way were invited to attend a clinic at the Chao Yang Men Hospital, Beijing, at some point during a 9-month period in 1995–1996. Of these 725 persons, 627 (86%) agreed to take part in the study. They were the offspring of 541 mothers.

Participants attended the clinic after a 12-hour overnight fast. Fasting blood samples were taken to measure levels of plasma glucose, insulin, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Six hundred fifteen participants received a 75-g oral glucose load, and additional blood samples were taken 2 hours later to measure levels of plasma glucose and insulin. Glucose tolerance testing was not done in 11 persons who were already known to be diabetic and 1 person who declined testing.

Plasma glucose levels were analyzed by using a standard glucose oxidase method (10). Plasma insulin levels were measured by using the Medgenix immunoassay (Medgenix Diagnostics, Fleurus, Belgium) (11, 12). Levels of serum total cholesterol, HDL cholesterol, and triglycerides were measured by using standard enzymatic methods (13–15). Measurements of glucose, insulin, and lipid levels were done at Addenbrooke's Hospital, Cambridge, United Kingdom. Serum low-density lipoprotein (LDL) cholesterol concentrations were also calculated (16). Blood pressure was measured with an automated recorder (Dinamap 8100, Critikon, Tampa, Florida) after the participants had been lying down for at least 5 minutes.

Height and weight were measured by one of two observers. We inquired about current occupation (classified as "manual" or "nonmanual") and average household income per capita. The clinic staff were unaware of any obstetric information about the participants and their mothers. Before the study began and twice during the study, the procedures used to obtain the measurements were standardized.

The study was approved by the Peking Union Medical College Ethical Committee. Participants gave informed verbal consent.

Statistical Analysis

Serum glucose levels, insulin levels, and triglyceride concentrations had skewed distributions and were therefore log-transformed to symmetry; they are presented as geometric means and SDs. We expressed each measurement of mother's weight as a Z-score of weight for gestational age, using a linear regression analysis of all of the mothers' weights with gestational age as the *x* variable. We averaged the Z-scores for weights that were recorded before and after 20 weeks of gestation and back-transformed the averages to obtain estimates of each mother's weight at 15 weeks of gestation (early pregnancy) and 38 weeks of gestation (late pregnancy). For each mother, we assessed weight gain in pregnancy by using linear regression analysis of the Z-scores and expressed the result as change in Z-score per week. In our analysis of the mothers' blood pressure, we used the antenatal measurement that was taken closest to 38 weeks of pregnancy.

We analyzed the relations among birth size, maternal size, and components of the insulin resistance syndrome by using tabulation of means, scatter plots, and multiple linear regression, in which the components of the insulin resistance syndrome in adult offspring were the dependent variables and the variables describing the mother or the offspring as an infant were the independent variables. Significance tests were based on linear regression with continuously measured variables. We used linear regression to adjust for confounding variables.

Results

The 627 participants ranged in age from 41 to 47 years (mean age, 45 years). Anthropometric and other descriptive data on participants as adults, participants at birth, and participants' mothers are shown in **Table 1**. Forty percent of the mothers

were primiparous. The 627 participants were 109 g heavier and 0.5 cm longer at birth than the 1294 adult offspring who did not participate, and their mothers were 0.1 cm shorter and 1.6 kg lighter at 38 weeks' gestation.

Associations of Components of the Insulin Resistance Syndrome with Participants' Body Size at Birth

Mean systolic and diastolic blood pressures were higher in men than in women ($P < 0.001$) (**Table 1**). After adjustment for sex, systolic blood pressure increased by 1.6 mm Hg (95% CI, 1.2 to 2.0 mm Hg) with every unit increase in body mass index (kg/m^2); diastolic blood pressure increased by 1.2 mm Hg (CI, 0.7 to 1.7 mm Hg). We adjusted blood pressure for sex and body mass index. Adjusted systolic and diastolic blood pressures were inversely related to birthweight (**Table 2**). A 1-kg increase in birthweight was associated with a 2.9-mm Hg (CI, 0.3 to 5.4 mm Hg) decrease in systolic blood pressure and a 1.7-mm Hg (CI, -0.05 to 3.5 mm Hg) decrease in diastolic blood pressure. This association was similar in men and women.

Systolic and diastolic blood pressure were not related to length of gestation. The systolic blood pressure of the mother was positively related to that of the offspring. For every 10-mm Hg increase in mother's systolic blood pressure during pregnancy, the adult offspring's systolic blood pressure increased by 1.3 mm Hg (CI, 0.5 to 2.2 mm Hg). However, the associations between birthweight and adult offspring's blood pressure were independent of the mother's systolic blood pressure. Systolic blood pressure increased with age in women (2.0 mm Hg [CI, 0.7 to 3.3 mm Hg] each year) but not in men. After adjustment for age, the association of adult offspring's blood pressure with birthweight remained statistically significant (adjusted coefficients,

Table 2. Mean Values of Components of the Insulin Resistance Syndrome, according to Birthweight*

| Variable | Birthweight | | | | | P Value† |
|--|-------------|-----------------|-----------------|------------|-------------|----------|
| | ≤2.5 kg | >2.5 to ≤3.0 kg | >3.0 to ≤3.5 kg | >3.5 kg | All Weights | |
| Participants, <i>n</i> | 44 | 184 | 284 | 115 | 627 | |
| Systolic blood pressure, <i>mm Hg</i> | 128 | 125 | 125 | 122 | 125 | 0.03 |
| Diastolic blood pressure, <i>mm Hg</i> | 79 | 75 | 76 | 74 | 75 | 0.06 |
| Fasting glucose level, <i>mmol/L (mg/dL)‡</i> | 5.7 (103) | 5.5 (99) | 5.3 (95) | 5.2 (94) | 5.4 (97) | 0.04 |
| 2-hour glucose level, <i>mmol/L (mg/dL)‡</i> | 7.9 (142) | 7.1 (128) | 6.3 (113) | 6.1 (110) | 6.6 (119) | 0.03 |
| Fasting insulin level, <i>pmol/L‡</i> | 46 | 47 | 44 | 33 | 43 | 0.009 |
| 2-hour insulin level, <i>pmol/L‡</i> | 317 | 314 | 218 | 201 | 245 | 0.02 |
| Triglyceride level, <i>mmol/L (mg/dL)‡</i> | 1.77 (157) | 1.38 (122) | 1.23 (109) | 1.02 (90) | 1.26 (112) | 0.008 |
| Total cholesterol level, <i>mmol/L (mg/dL)</i> | 5.15 (199) | 4.93 (191) | 4.98 (193) | 4.84 (187) | 4.95 (192) | 0.2 |
| LDL cholesterol level, <i>mmol/L (mg/dL)</i> | 3.05 (118) | 2.93 (113) | 2.93 (113) | 2.83 (110) | 2.92 (113) | 0.1 |
| HDL cholesterol level, <i>mmol/L (mg/dL)</i> | 1.35 (52) | 1.33 (51) | 1.38 (53) | 1.41 (55) | 1.37 (53) | 0.03 |

* Values are adjusted for sex and body mass index. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† Based on linear regression with continuously measured variables.

‡ Values are geometric means.

−3.0 mm Hg/kg for systolic blood pressure and −1.9 mm Hg/kg for diastolic blood pressure).

Sixteen adult offspring were found to have type 2 diabetes mellitus (17 (2-hour plasma glucose level ≥ 11.1 mmol/L [≥ 200 mg/dL]), 11 adult offspring were already known to have type 2 diabetes mellitus, and 120 adult offspring (64 men and 56 women) were found to have impaired glucose tolerance (2-hour plasma glucose level, 7.8 to 11.0 mmol/L [14 to 198 mg/dL]). The mean body mass index was 25.4 kg/m² in the 147 adult offspring who had impaired glucose tolerance or type 2 diabetes mellitus and 23.6 kg/m² in the remainder of participants. Fasting glucose levels were 3.8% (CI, 1.7% to 5.8%) higher in men than in women, and insulin levels were 9.5% (CI, 1.8% and 16.2%) higher in men than in women. Two-hour plasma glucose levels were 2.6% (CI, −1.6% to 7.0%) lower in men than in women, and 2-hour insulin levels were 16.8% (CI, 3.5% to 31.9%) lower in men than in women.

After adjustment for sex, fasting and 2-hour plasma glucose and insulin levels increased with increasing body mass index. For every unit increase in body mass index, plasma levels increased by 1.0% (CI, 0.7% to 1.3%) for fasting glucose level, by 2.5% (CI, 1.8% to 3.1%) for 2-hour glucose level, by 9.7% (CI, 8.5% to 11.0%) for fasting insulin level, and by 9.8% (CI, 7.8% to 11.9%) for 2-hour insulin level. We therefore adjusted values for body mass index and sex. Fasting and 2-hour plasma glucose and insulin levels decreased with increasing birthweight (Table 2). For every 1-kg increase in birthweight, fasting glucose level decreased by 2.4% (CI, 0.1% to 4.7%), 2-hour glucose level decreased by 5.1% (CI, 0.7% to 9.3%), fasting insulin level decreased by 9.7% (CI, 2.5% to 16.5%), and 2-hour insulin level decreased by 14.0% (CI, 2.4% to 24.2%). These associations were similar in men and women. Glucose and insulin levels were not related to duration of gestation.

Serum levels of triglycerides, total cholesterol, and LDL cholesterol were higher in men than in women (by 30.2% [CI, 24.3% to 35.5%], 0.3 mmol/L [CI, 0.2 to 0.5 mmol/L], and 0.3 mmol/L [CI, 0.2 to 0.5 mmol/L], respectively). After adjustment for sex, serum concentrations increased with increasing body mass index. For every unit increase in body mass index, serum concentrations increased by 6.4% (CI, 5.2% to 7.7%) for triglycerides, 0.04 mmol/L (2 mg/dL) (CI, 0.01 to 0.06 mmol/L [0.4 to 2 mg/dL]) for total cholesterol, and 0.04 mmol/L (2 mg/dL) (CI, 0.02 to 0.06 mmol/L [1 to 2 mg/dL]) for LDL cholesterol. Serum HDL cholesterol concentrations were 0.29 mmol/L (11 mg/dL) (CI, 0.23 to 0.34 mmol/L [9 to 13 mg/dL]) lower in men than in women.

After adjustment for sex, serum HDL cholesterol

concentrations decreased by 0.045 mmol/L (2 mg/dL) (CI, 0.037 to 0.053 mmol/L [1 to 2 mg/dL]) for every unit increase in body mass index. We adjusted serum lipid concentrations for body mass index and sex. Similar to 2-hour plasma glucose and insulin levels, serum triglyceride levels decreased with increasing birthweight (Table 2) and were not related to length of gestation. In contrast, concentrations of total cholesterol and LDL cholesterol were not significantly related to birthweight, and concentrations of HDL cholesterol increased with increasing birthweight (Table 2). The associations between birthweight and serum lipid concentrations were similar in men and women. Serum concentrations of total cholesterol and HDL cholesterol were not related to length of gestation, whereas concentrations of LDL cholesterol decreased by 0.004 mmol/L (0.2 mg/dL) (CI, 0.008 to 0.0 mmol/L [0.3 to 0.0 mg/dL]) with each day-long increase in gestation.

The results shown in Table 2 were similar for the offspring of primiparous and multiparous women, although the relations of birthweight to systolic blood pressure, 2-hour plasma insulin levels, and serum LDL and HDL cholesterol concentrations were stronger in the offspring of primiparous women. Inclusion of length of gestation and birthweight in a simultaneous regression analysis generally increased the magnitude of the regression coefficient of each outcome on birthweight (except for HDL cholesterol level, for which the coefficient decreased by less than 10%).

Analysis of the relations of the components of the insulin resistance syndrome to participants' current occupation, fathers' occupation, or average household income per capita showed no consistent or statistically significant patterns, with the exception of systolic and diastolic blood pressures (which were higher in participants who currently had manual occupations). After adjustment for current occupation, the effect of the relation between systolic blood pressure and birthweight decreased by 11% but remained statistically significant. Similar adjustment did not change the relation between diastolic blood pressure and birthweight.

Association of Components of the Insulin Resistance Syndrome with Mothers' Body Size

Between 15 and 38 weeks of pregnancy, mothers gained an average of 9.6 kg in weight and 4.0 kg/m² in body mass index. As expected, birthweight was positively related to mother's weight in early and late pregnancy, increasing by 21 g (CI, 16 to 26 g) for every 1-kg increase in mother's weight at 38 weeks and by 22 g (CI, 13 to 31 g) for every 1-kg increase in mother's weight at 15 weeks. Birthweight increased by 13 g (CI, 7 to 18 g) for every 1-cm increase in mother's height and by 35 g (CI, 21 to

Table 3. Mean Values of Components of the Insulin Resistance Syndrome, according to Maternal Body Mass Index at 15 and 38 Weeks of Pregnancy*

| Variable | Maternal Body Mass Index at 15 Weeks of Pregnancy | | | | | P Value† | Maternal Body Mass Index at 38 Weeks of Pregnancy | | | | | P Value† |
|---|---|----------------------------------|----------------------------------|-------------------------|------------|----------|---|--------------------------------|--------------------------------|-----------------------|------------|----------|
| | ≤19.2 kg/m ² | >19.2 to ≤20.5 kg/m ² | >20.5 to ≤22.3 kg/m ² | >22.3 kg/m ² | All | | ≤23 kg/m ² | >23 to ≤24.5 kg/m ² | >24.5 to ≤26 kg/m ² | >26 kg/m ² | All | |
| Participants, <i>n</i> | 56 | 57 | 57 | 56 | 226 | | 119 | 161 | 154 | 150 | 584 | |
| Systolic blood pressure, mm Hg | 125 | 122 | 125 | 124 | 124 | >0.2 | 125 | 124 | 126 | 124 | 125 | >0.2 |
| Diastolic blood pressure, mm Hg | 74 | 73 | 76 | 75 | 75 | >0.2 | 75 | 75 | 77 | 75 | 75 | >0.2 |
| Fasting glucose level, mmol/L (mg/dL)‡ | 5.2 (94) | 5.3 (95) | 5.3 (95) | 5.3 (95) | 5.3 (95) | >0.2 | 5.3 (95) | 5.3 (95) | 5.5 (99) | 5.3 (95) | 5.4 (97) | 0.2 |
| 2-hour glucose level, mmol/L (mg/dL)‡ | 7.4 (133) | 7.0 (126) | 7.1 (128) | 5.6 (101) | 6.7 (121) | 0.008 | 7.6 (137) | 6.6 (119) | 6.7 (121) | 5.7 (103) | 6.6 (119) | 0.003 |
| Fasting insulin level, pmol/L‡ | 49 | 50 | 41 | 40 | 45 | 0.07 | 44 | 50 | 40 | 39 | 43 | 0.1 |
| 2-hour insulin level, pmol/L‡ | 399 | 299 | 252 | 181 | 273 | 0.02 | 304 | 277 | 282 | 177 | 254 | 0.007 |
| Triglyceride level, mmol/L (mg/dL)‡ | 1.56 (138) | 1.37 (121) | 1.10 (97) | 1.07 (95) | 1.26 (112) | 0.06 | 1.37 (121) | 1.38 (122) | 1.32 (117) | 1.05 (93) | 1.27 (113) | 0.1 |
| Total cholesterol level, mmol/L (mg/dL) | 5.21 (202) | 4.81 (186) | 4.78 (185) | 4.77 (185) | 4.89 (189) | 0.02 | 4.99 (193) | 5.01 (194) | 4.96 (192) | 4.83 (187) | 4.95 (192) | 0.2 |
| LDL cholesterol level, mmol/L (mg/dL) | 3.14 (122) | 2.70 (104) | 2.80 (108) | 2.76 (107) | 2.85 (110) | 0.01 | 2.95 (114) | 2.94 (114) | 2.89 (112) | 2.86 (111) | 2.91 (113) | >0.2 |
| HDL cholesterol level, mmol/L (mg/dL) | 1.35 (52) | 1.42 (55) | 1.35 (52) | 1.41 (55) | 1.38 (53) | >0.2 | 1.36 (53) | 1.36 (53) | 1.38 (53) | 1.38 (53) | 1.37 (53) | >0.2 |

* Values are adjusted for sex and body mass index. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

† Based on linear regression with continuously measured variables.

‡ Values are geometric means.

50 g) and 30 g (CI, 8 to 53 g) for every kg/m² increase in mother's body mass index at 15 and 38 weeks of pregnancy, respectively.

Table 3 shows the components of the insulin resistance syndrome in adult offspring according to mother's body mass index at 38 weeks of pregnancy. Blood pressure was not related to mother's body mass index. In contrast, 2-hour plasma glucose and insulin levels decreased with increasing mother's body mass index. Similar trends in fasting insulin levels and serum triglyceride levels were of borderline statistical significance. To determine the separate effects of mother's body mass index and birthweight on 2-hour plasma glucose levels and insulin levels in adult offspring, we performed simultaneous regression analysis and found that the trends remained for both ($P = 0.01$ for the relation between mother's body mass index and glucose level, $P = 0.04$ for the relation between birthweight and glucose level, $P = 0.02$ for the relation between mother's body mass index and insulin level, and $P = 0.08$ for the relation between birthweight and insulin level). Mother's body mass index in late pregnancy was not related to the offspring's serum cholesterol concentrations (**Table 3**).

The associations between plasma glucose levels, insulin levels, and triglyceride concentrations and mother's body mass index at 15 weeks of pregnancy were similar to those seen at 38 weeks of pregnancy (**Table 3**). However, statistically significant decreases were seen in serum concentrations of total and LDL cholesterol when we compared them with increasing

mother's body mass index at 15 weeks of pregnancy (**Table 3**). We examined associations with mother's body mass index at 38 weeks of pregnancy in the subgroup of mothers whose body mass indexes at 15 weeks were known. In this subgroup, body mass index at 38 weeks of pregnancy was not associated with serum cholesterol level. We found no relation between maternal weight gain in pregnancy and components of the insulin resistance syndrome. The results in **Table 3** were similar for primiparous and multiparous mothers.

Discussion

We found that infants with low birthweights had elevated levels of the components of the insulin resistance syndrome in adult life. They had higher blood pressure, elevated plasma glucose and insulin levels (both fasting and after a standard oral glucose load), and elevated plasma triglyceride concentrations (**Table 2**). Lower birthweight was associated with lower serum concentrations of HDL cholesterol, but there was no relation with LDL cholesterol. The offspring of women with a low body mass index in pregnancy had elevated 2-hour plasma insulin levels as adults, which suggests that they were insulin-resistant (**Table 3**). They also had reduced glucose tolerance.

In general, the associations between birthweight and the components of the insulin resistance syndrome found in our study are similar to those ob-

served in developed countries (5–7). An association between decreased birthweight and elevated blood pressure has been consistently observed in several countries, and the size of the association in our study is similar to that in other populations (18). As in other studies in children, we found that the associations between birthweight and blood pressure were independent of mother's blood pressure during pregnancy (19, 20). We are unaware of any comparable studies in adults.

The association of lower birthweight with elevated plasma glucose and insulin levels, both fasting and after a standard oral glucose load, is consistent with findings in the United Kingdom and Sweden (5, 6, 21–24). As in other studies, we found that lower birthweight was associated with elevated plasma triglyceride concentrations (5) and low serum concentrations of HDL cholesterol (25, 26), although we did not find an association between birthweight and LDL cholesterol concentrations (Table 2).

In a follow-up study in Finland, men born to mothers of short stature (<1.58 m) who had a body mass index in late pregnancy of 30 kg/m² or more were three times as likely to die of coronary heart disease than men whose mothers' body mass index was 24 kg/m² or less (27). In our study, 2-hour plasma glucose and insulin levels tended to be highest in the offspring of mothers who had a low body mass index in late pregnancy (Table 3). This suggests that thinness of the mother during pregnancy is associated with insulin resistance and reduced glucose tolerance in adult offspring. The difference between our results and those of the Finnish study may be due to the fact that the populations of China and Finland are at different stages of nutritional transition; mothers in our study had much lower mean body mass indexes. Alternately, these differences may have arisen because of the different outcomes studied or because of differences in genetic susceptibility.

We found that mother's body mass index was not related to the adult offspring's blood pressure. We are unaware of any other studies in adults. In three studies of children or adolescents, blood pressure was not associated with mother's body mass index (28–30), although two studies reported an association between elevated blood pressure and low maternal skinfold thickness (28, 29). Mother's body mass index in late pregnancy was not related to serum cholesterol concentrations in the adult offspring, whereas low maternal body mass index in early pregnancy was associated with elevated serum concentrations of LDL and total cholesterol. This association has not previously been reported, and we cannot explain it.

We examined men and women who were born in

Beijing, China, from 1948 to 1954, when much of the population was chronically malnourished. The persons born in the Peking Union Medical College Hospital were not representative of all persons born in the city. However, the short stature and thinness of the mothers in our sample and the small size of their babies are in accord with the results of contemporary anthropometric surveys done in China; in addition, these characteristics are typical of persons in chronically malnourished communities (31–33).

Approximately half of the mothers for whom we obtained obstetric records were still living in Beijing at the time of our study. Through them, we were able to trace and examine 33% (627 of 1921) of their eligible adult offspring. Offspring who were examined were slightly heavier and longer at birth than those who were not examined. These small differences might be explained by higher infant mortality rates among smaller babies. The fact that the sample was not representative would introduce a bias only if the relation of birthweight or maternal body mass index to components of the insulin resistance syndrome differed between persons born in the hospital and those born outside it, between those who were traced and those who were not traced, or between those who came to the clinic and those who did not. However, we cannot assess this further.

Our study used observational data and demonstrated relations among mother's body mass index in pregnancy, birthweight, and components of the insulin resistance syndrome. These associations were not necessarily causal. Even if these associations are subsequently proven to be causal, they may not be a sufficient basis for preventive action. Nevertheless, experimental studies on this topic in humans are unlikely to be ethical or practical, particularly during the long latent period from fetal life to adult development of disease. We believe that observational studies such as ours can increase understanding of the causes of the insulin resistance syndrome and lead to the development of preventive action.

A mother's body mass index in late pregnancy reflects both weight gain during pregnancy and body mass index before pregnancy. We found that the associations of insulin and glucose levels in the offspring with mother's body mass in early and late pregnancy were similar (Table 3), but we did not find any associations of these variables with mother's weight gain in pregnancy. This suggests that in our sample, insulin resistance was associated with a low maternal body mass in early pregnancy, which in turn probably reflects a low body mass around the time of conception.

Body mass index measures both lean body mass and fat mass. Mothers with a low lean body mass have a low protein turnover, which reduces the

availability of amino acids to the fetus (34). Similarly, a low maternal fat mass reduces the availability of fatty acids to the fetus. We speculate that insulin resistance may originate through fetal undernutrition caused by low maternal protein or fatty acid stores.

We used maternal anthropometric data to measure maternal nutritional status. We did not have data on mothers' diets before or during pregnancy. However, diet during pregnancy may influence the fetus' nutrition without greatly affecting its growth rate. Even the severe wartime famine in the Netherlands reduced birthweight by only 250 g (35). However, a recent study found that men and women who were exposed to the Dutch famine in utero were insulin-resistant and had reduced glucose tolerance. This suggests that fetal adaptations to undernutrition may permanently change metabolism without reducing rates of growth or size at birth. Observations in animals support this conclusion (36). Similarly, in our study a low maternal body mass index had an effect on glucose-insulin metabolism that was independent of its effect on birthweight.

The men and women in our study lived through a period of nutritional transition and were born to mothers who were stunted and thin (presumably because of chronic malnutrition). However, although our participants were relatively short in stature, their body mass indexes as adults approached those of adults in the United Kingdom. Elevated plasma insulin levels, reduced glucose tolerance, and hypertriglyceridemia in the offspring were associated with low body mass index in the mothers and high adult body mass index. Therefore, prevention of adult obesity remains an important strategy for decreasing the incidence of the insulin resistance syndrome, particularly in the immediate future. Our study suggests that in the longer term, benefit may also be derived from increasing women's body mass index to optimal levels before pregnancy. Promotion of maternal nutrition may also offer additional, more immediate benefits to mother and infant.

From Peking Union Medical College, Beijing, People's Republic of China; and Southampton General Hospital, Southampton, United Kingdom.

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Requests for Single Reprints: Catherine Law, MD, MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO16 6YD, United Kingdom.

Requests To Purchase Bulk Reprints (minimum, 100 copies): Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

Current Author Addresses: Drs. Mi and Zhang: Department of Epidemiology, Peking Union Medical College, 5 Dong Dan San Tiao, Beijing 100005, People's Republic of China.

Drs. Law, Osmond, and Barker: MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO16 6YD, United Kingdom.

Dr. Stein: Department of Public Health Medicine, Southampton and South West Hants Health Authority, Oakley Road, Southampton, Hampshire S016 49X, United Kingdom.

Author Contributions: Conception and design: J. Mi, C. Law, K.-L. Zhang, C. Osmond, C. Stein, D. Barker.

Analysis and interpretation of the data: J. Mi, C. Law, K.-L. Zhang, C. Osmond, C. Stein, D. Barker.

Drafting of the article: J. Mi, C. Law, K.-L. Zhang, C. Osmond, C. Stein, D. Barker.

Final approval of the article: J. Mi, C. Law, K.-L. Zhang, C. Osmond, C. Stein, D. Barker.

Statistical expertise: C. Osmond.

Administrative, technical, or logistic support: K.-L. Zhang.

Collection and assembly of data: J. Mi, C. Law, C. Stein.

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