Evidence of a Relationship Between Infant Birth Weight and Later Diabetes and Impaired Glucose Regulation in a Chinese Population

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OBJECTIVE — The aim of this study was to determine the influence of birth weight, a marker of fetal growth, on the development of later impaired glucose metabolism throughout the life span of people living in China.

RESEARCH DESIGN AND METHODS — We recorded detailed anthropometric data including height, weight, and health status and measured blood glucose levels and insulin concentrations after fasting and at 120 min of a standard oral glucose tolerance test from 2,019 eligible subjects born between 1921 and 1954 to investigate the risk of developing type 2 diabetes and impaired glucose regulation (IGR).

RESULTS — The diabetes and IGR groups were characterized by significantly lower birth weight ($P < 0.001$), smaller head circumference ($P < 0.001$), smaller ponderal index ($P = 0.007$), and shorter length ($P = 0.004$) compared with those in the normal glucose tolerance group. Using multiple logistic regression analysis, we observed that birth weight remained significantly associated with diabetes and IGR after adjustments for possible confounding variables at birth and in adult life such as sex, age, central obesity, smoking status, alcohol consumption, dyslipidemia, family history of diabetes, and occupational status ($P = 0.027$). There was a significantly increased risk of getting diabetes and IGR for those with low birth weight (odds ratio 1.748 [95% CI 1.018–3.001], $P = 0.043$).

CONCLUSIONS — The results confirm that lower birth weight is an independent risk factor for later diabetes or IGR and show for the first time that this risk factor also applies for a Chinese population.

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; IGR, impaired glucose regulation; NGT, normal glucose tolerance; PUMCH, Peking Union Medical College Hospital.

Most chronic noncommunicable diseases originate as a result of the joint effects of genetic and environmental risk factors. Traditionally, risk factors associated with adult lifestyle, such as smoking, diet, and exercise habits, have attracted a great deal of interest. In more recent years, attention has also been paid to distal risk factors in early life. The intrauterine environment is now generally accepted as an important determinant of risk of disease in adulthood. The classic study by Hales et al. (1) was the first to show that people with low birth weight had higher rates of type 2 diabetes later in life. Many studies have demonstrated an inverse relationship between body size at birth, as a marker of fetal growth, and diabetes or impaired glucose tolerance in adult life (2–10). However, many of these studies include only a few hundred individuals from developed countries (U.S. and Europe) (2–5). Few studies have been published exploring the relationship between intrauterine growth retardation and impaired glucose metabolism in later life in developing countries.

It is important to understand determinants of chronic diseases and health at later ages because populations in most countries are aging. China's population, in particular, is aging at an extraordinarily rapid pace. Since the early 20th century, Chinese people have lived through frequent famines, civil wars, and invasions. Nutritional impairment in utero because of poor nutrition of the mother, in concert with the development of the energy-dense and Westernized diet and lifestyle of adults today, could lead to adverse health trends. To date, however, there have been few studies from developing countries, including China, to test the fetal origins hypothesis. Thus, research on the relationship between intrauterine growth retardation and impaired glucose metabolism for Chinese people born 50–70 years ago is of particular significance.

We report the results of a follow-up

Table 1—*Means and ANOVA tests for baseline characteristics of the study subjects*

Variable	Diabetes	IGR	NGT	F/χ^2	*P* value
n	391	564	1,064		
Measurements at birth					
Birth weight (g)*	3,015.62 ± 469.01 (391)	3,091.09 ± 436.61 (558)	3,153.88 ± 459.09 (1,055)	13.803	<0.001
Birth length (cm)	49.05 ± 2.50 (388)	49.47 ± 2.26 (560)	49.52 ± 2.48 (1,055)	5.488	0.004
Head circumference (cm)*	31.32 ± 1.64 (390)	31.53 ± 1.75 (555)	31.79 ± 1.63 (1,047)	12.057	<0.001
Ponderal index (kg/m^3)†	25.51 ± 3.11 (388)	25.56 ± 3.57 (557)	26.01 ± 3.36 (1,052)	4.939	0.007
Gestational weeks	39.05 ± 2.10 (379)	39.21 ± 1.99 ((545)	39.25 ± 2.14 (1,037)	1.269	0.281
Number of pregnancies‡	3.08 ± 2.37 (383)	2.78 ± 2.05 (551)	2.78 ± 2.12 (1,042)	3.549	0.094
Placental weight (g)	539.90 ± 122.37 (363)	532.82 ± 112.64 (525)	548.27 ± 125.13 (980)	2.863	0.057
Parity‡	2.80 ± 2.11 (382)	2.50 ± 1.84 (551)	2.49 ± 1.83 (1,042)	5.628	0.060
Adult measurements					
HOMA-IR‡	3.84 ± 4.24 (378)	2.39 ± 2.03 (562)	1.49 ± 1.08 (1,056)	340.783	<0.001
Waist circumference	92.14 ± 10.1 (367)	91.208 ± 10.6 (539)	86.89 ± 10.5 (1,022)	47.956	<0.001
BMI (kg/m^2)	25.87 ± 3.74 (373)	25.53 ± 3.45 (550)	24.38 ± 3.40 (1,064)	34.864	<0.001
Age*	62.49 ± 7.89 (384)	60.99 ± 8.26 (564)	57.61 ± 7.70 (1,064)	67.842	<0.001

Data are means ± SD (*n*). *Significant difference between diabetes and IGR, between diabetes and NGT, or between IGR and NGT. †Ponderal index: birth weight/length^3. ‡Kruskal-Wallis test. The statistical tests of the difference among the diabetes, IGR, and NGT groups in this table are not adjusted for confounding factors.

study of people born in Peking Union Medical College Hospital (PUMCH) between 1921 and 1954. The study includes a quite large population of elderly and middle-aged individuals and extensive data on a wide range of dimensions at birth, gestational period, and adult life. To test the fetal origin hypothesis, we paid particular attention to the interaction of early and later life factors.

RESEARCH DESIGN AND METHODS

— The PUMCH in Beijing routinely keeps detailed obstetric records. Data include weight, length, head circumference at birth, placental weight, weeks of gestation, blood pressure at delivery and during the pregnancy, maternal parity, age, date of last menstrual period, and so on. Authorities at PUMCH allowed us to examine obstetric records of all 12,097 babies born there from 1921 to 1954. We submitted their birth records identification data to the Beijing Population Registry Office and found 2,085 individuals who were alive when the present study was conducted. The vast majority of them were living in the Beijing area. We recruited voluntary participants from these 2,085 individuals. The Peking Union Medical College Ethical Committee approved the study, and the study protocol was reviewed and approved by the National Institutes of Health scientific review committee. All participants provided informed consent. We subsequently contacted the 2,019 participants who agreed to take part in the study and performed a

Table 2—*Association of neonatal characteristics with impaired glucose metabolism (Pearson χ^2 tests)*

Variable	Diabetes	IGR	NGT	χ^2	*P* value
	391	564	1,064		
Birth weight				31.377	<0.001
<2,500 g	47 (29.2)	42 (26.1)	72 (44.7)		
2,500–3,000 g	146 (23.2)	189 (30.1)	293 (46.7)		
3,000–3,500 g	132 (16.2)	226 (27.7)	457 (56.1)		
>3,500 g	66 (16.5)	101 (25.3)	233 (58.3)		
Ponderal index				18.616	0.017
<2.2 kg/m^3	34 (24.3)	43 (30.7)	63 (45.0)		
2.2–2.4 kg/m^3	84 (23.1)	112 (30.9)	167 (46.0)		
2.4–2.6 kg/m^3	119 (18.9)	177 (28.2)	332 (52.9)		
2.6–2.8 kg/m^3	83 (15.7)	140 (26.5)	306 (57.8)		
>2.8 kg/m^3	68 (20.2)	85 (25.2)	184 (54.6)		
Birth length				14.456	0.071
<48 cm	94 (22.4)	110 (26.3)	215 (51.3)		
48–49 cm	60 (21.0)	74 (25.9)	152 (53.1)		
49–50 cm	83 (22.9)	97 (26.7)	183 (50.4)		
50–51 cm	60 (17.2)	110 (31.5)	179 (51.3)		
>51 cm	91 (15.5)	169 (28.8)	326 (55.6)		
Head circumference				28.757	<0.001
<31 cm	133 (24.2)	155 (28.2)	262 (47.6)		
31–33 cm	84 (18.7)	294 (29.9)	505 (51.4)		
>33 cm	73 (15.9)	106 (23.1)	280 (61.0)		
Placental weight				8.799	0.368
<450 g	67 (20.1)	99 (29.7)	167 (50.2)		
450–525 g	128 (21.2)	169 (27.9)	308 (50.9)		
525–600 g	81 (17.4)	143 (30.8)	241 (51.8)		
600–675 g	45 (17.4)	63 (24.4)	150 (58.1)		
>675 g	42 (20.3)	51 (24.6)	114 (55.1)		
Biparietal/birth length				3.858	0.426
<0.18	85 (16.5)	149 (28.9)	281 (54.6)		
0.18–0.2	249 (20.0)	347 (27.9)	647 (52.1)		
>0.2	50 (21.6)	62 (26.8)	119 (51.5)		
Gestational weeks				6.947	0.139
Full term	327 (18.8)	487 (28.0)	924 (53.2)		
Premature birth	36 (26.3)	39 (28.5)	62 (45.3)		
Post-term pregnancy	16 (18.6)	19 (22.1)	51 (59.3)		

The estimates of the association in this table are not adjusted for confounding factors.

Table 3—*Logistic analyses of the relationship between peripartum characteristics and risk of impaired glucose metabolism in adulthood, adjusted for confounders at birth*

Variable	*n*	OR	SE	95% CI	*P* value
Sex (vs. male)	876				0.46
Female	896	0.820	0.100	0.674–0.997	
Birth weight (vs. 3,000–3,500 g)	724				<0.001
<2,500 g	135	1.985	0.232	1.260–3.129	0.003
2,500–3,000 g	552	1.849	0.141	1.404–2.436	<0.001
>3,500 g	361	0.976	0.154	0.722–1.318	0.872
Placental weight (vs. 525–600 g)	440				0.560
<450 g	318	0.833	0.161	0.608– 1.143	0.258
450–525 g	572	0.915	0.132	0.706–1.186	0.503
600–675 g	246	0.785	0.167	0.566–1.088	0.146
>675 g	196	0.815	0.182	0.570–1.164	0.260
Head circumference (vs. 31–33 cm)	878				0.002
<31 cm	480	1.141	0.127	0.889–1.464	0.300
>33 cm	414	0.667	0.132	0.515–0.865	0.002
Gestational hypertension (vs. no)	1,566		0.154		0.473
Yes	206	0.895		0.662–1.211	
Maternal age (vs. 21–35 years)	1,449				0.792
<21 years	156	0.929	0.179	0.654–1.318	0.679
>35 years	167	1.102	0.184	0.769–1.579	0.598
Parity (vs. 1)	711				0.116
2–3	637	1.106	0.117	0.880–1.391	0.387
4–5	264	1.121	0.156	0.826–1.521	0.465
>6	160	1.626	0.200	1.098–2.409	0.015

follow-up during May 2003 and April 2005.

Measurements

A team consisting of trained and certified doctors, nurses, and technicians performed all measurements. An interview was conducted with each subject to determine history of chronic diseases and current health status using standardized procedures. Information on adult life status, including current occupation, smoking status, alcohol consumption, and family history of diabetes, was obtained through questionnaires. Height, weight, waist circumference, and blood pressure were also measured. The clinic staff was unaware of any obstetric information about the participants and their mothers. During the health examinations, blood samples were collected from the participants.

Participants attended the clinic after a 12-h overnight fast. Then blood samples were drawn to measure plasma concentrations of glucose and insulin and serum levels of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. Additional blood samples at 120 min after a standard (75 g) oral glucose load were also taken to measure plasma levels of glucose and insulin. Oral glucose tolerance testing (75 g) was not performed in those individuals in whom diabetes had already been diagnosed.

Dyslipidemia was defined as the presence of one or more of the following: triglycerides ≥150 mg/dl, total cholesterol ≥220 mg/dl, HDL cholesterol ≤40 mg/dl, or LDL cholesterol ≥100 mg/dl. Hypertension was defined as the presence of one or more of the following: systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or a definite history of hypertension with or without medicine. Diabetes was defined as the presence of one or more of the following: fasting plasma glucose ≥7.0 mmol/l, glucose at 120 min ≥11.1 mmol/l, or a definite history of diabetes with or without medicine. The criteria (11) for impaired glucose regulation (IGR) were a fasting plasma glucose level of ≥5.6 to <7.0 mmol/l and/or a 2-h plasma glucose level on the oral glucose tolerance test of ≥7.8 to <11.1 mmol/l. Central obesity was defined as waist circumference ≥90 cm for men and ≥80 cm for women, according to the International Diabetes Federation's proposed definition of the metabolic syndrome in 2005 (12). Insulin resistance was determined by homeostasis model assessment (HOMA-IR): HOMA-IR = fasting plasma glucose (millimoles per liter) × fasting plasma insulin (picomoles per liter)/22.5 (13).

Statistical analysis

Results are expressed as means ± SD. Differences among groups were assessed by ANOVA for normally distributed continuous variables, by nonparametric tests (Kruskall-Wallis test) for non-normally distributed continuous variables (HOMA-IR, the number of pregnancies, and parity), and by χ^2 tests for discrete variables. We analyzed the data derived from the birth records, clinic examinations, and interviews, using multivariate logistic regression models and controlling for possible confounding factors. In our logistic regression models, impaired glucose metabolism in adult life was the dependent variable, and mothers' status, measurements at birth, and adult status such as smoking status, alcohol consumption, and family history of diabetes were the independent variables. Impaired glucose metabolism is defined as having either type 2 diabetes or IGR. All statistics were run on SPSS 12.0 for Windows (SPSS, Chicago, IL).

RESULTS — Among a total of 2,019 subjects, 1,064 had normal glucose tolerance (NGT), whereas 391 and 564 individuals were found to exhibit type 2 diabetes (19.4%) and IGR (27.9%), respectively. Of those, 54 were already known to have type 2 diabetes and received antidiabetes treatment before the present study.

Table 1 shows the baseline characteristics of the study subjects and the statistical test of the differences between the diabetes, IGR, and NGT groups, not adjusted for confounding factors. There were no significant sex differences among the three groups (not shown). However, there were significant age differences ($P < 0.001$). The mean gestational weeks, parity, placental weight, and number of pregnancies were similar in all three groups. There were large differences related to birth weight, length, head circumference, and ponderal index among the three groups. The diabetes and IGR groups were associated with significantly lower birth weight ($P < 0.001$), smaller head circumference ($P < 0.001$), smaller ponderal index ($P < 0.001$), and shorter length ($P = 0.004$) in contrast with the NGT group.

The association between maternal and neonatal characteristics and diabetes and IGR, without controls for confound-

Table 4—*Predictive factors for the presence of impaired glucose metabolism in adulthood, adjusted for confounders both at birth and in adulthood*

Variable	*n*	OR	SE	95% CI	*P* value
Age		1.063	0.008	1.046–1.081	<0.001
Sex (vs. male)	755	0.938	0.151	0.698–1.261	0.671
Birth weight (vs. 3,000–3,500g)	623				0.027
<2,500 g	112	1.748	0.276	1.018–3.001	0.043
2,500–3,000 g	489	1.625	0.166	1.174–2.249	0.003
>3,500 g	313	1.006	0.183	0.703–1.440	0.973
Placental weight (vs. 525–600 g)	377				0.666
<450 g	275	1.049	0.192	0.720–1.530	0.803
450–525 g	500	1.092	0.158	0.801–1.487	0.578
600–675 g	217	0.818	0.198	0.555–1.207	0.312
>675 g	168	0.894	0.217	0.584–1.368	0.605
Maternal age (vs. 21–35 years)	256				0.622
<21 years	137	0.814	0.212	0.537–1.232	0.330
>35 years	144	0.994	0.225	0.640–1.543	0.977
Parity (vs.1)	609				0.288
2–3	558	0.917	0.142	0.695–1.211	0.542
4–5	234	0.828	0.188	0.573–2.1196	0.314
>6	136	1.327	0.250	0.813–2.167	0.257
Gestational hypertension (vs. no)	1,356	0.891	0.183	0.622–1.277	0.530
Triglyceride (vs. <150 mg/dl)	941	1.791	0.124	1.404–2.284	<0.001
HDL cholesterol (vs. >40 mg/dl)	1,382	1.095	0.206	0.732–1.639	0.658
LDL cholesterol (vs. <100 mg/dl)	183	0.981	0.185	0.683–1.409	0.916
Hypertension (vs. no)	733	1.860	0.121	1.468–2.356	<0.001
Family history of diabetes (vs. no)	1,133	2.149	0.133	1.656–2.789	<0.001
Drinking (vs. no)	1,492	2.225	0.341	1.140–4.345	0.019
Central obesity (vs. no)	545	1.566	0.130	1.213–2.023	0.001
Smoking status (vs. never smoker)	1,108				0.551
Current smoke	271	0.961	0.182	0.673–1.374	0.829
Ex-smoker	158	1.223	0.213	0.807–1.855	0.343
Living alone (vs. no)	655	1.242	0.121	0.980–1.574	0.073
Job (current social class) (vs. physical labor)	543	1.083	0.236	0.682–1.719	0.578

Valid sample size = 1,772.

ing factors, is shown in Table 2. There was a powerful association between low birth weight, small length, head circumference, and ponderal index and diabetes and IGR (collectively referred to below as impaired glucose metabolism), whereas an inverse association between impaired glucose metabolism and four categories of birth weight and head circumference and five categories of PI was evident. No systematic effect regarding placental weight and gestational weeks was apparent.

In Tables 3 and 4, diabetes and IGR were combined as impaired glucose metabolism in the logistic regression analysis. After simultaneous adjustment for the perinatal confounding factors, as shown in the final column of Table 3, a significant association was identified only between birth weight and impaired glucose metabolism ($P < 0.001$). The risk of impaired glucose metabolism for those with low birth weight (<2,500 g) was nearly two times higher than that for those with normal birth weight. The effect of head circumference and ponderal index on impaired glucose metabolism was much attenuated and no longer significant ($P > 0.05$). Table 4 shows the strength of the association between impaired glucose metabolism and birth weight, controlling for possible confounding factors both at birth and in adulthood.

The present study showed that impaired glucose metabolism was significantly associated with facets of adult life status such as age, smoking, being overweight, family history of diabetes, hypertension, and dyslipidemia (results not shown). Furthermore, adjustment for possible confounding factors at birth and in adult life, such as sex, age, central obesity, smoking status, alcohol intake, hypertension, dyslipidemia, family history of diabetes, and occupational status, led to only a small reduction in the strength of the association between birth weight and impaired glucose metabolism (Table 4) ($P = 0.027$). Lower birth weight is an independent risk factor for impaired glucose metabolism in adult life (odds ratio 1.748, [95% CI 1.018–3.001], $P = 0.043$).

CONCLUSIONS — In this retrospective study, we explored the prevalence of IGR and diabetes in a quite large birth cohort of Chinese born in PUMCH between 1921 and 1954. There was little difference between men and women in the frequency of diabetes and IGR in this population. The prevalence of IGR (27.9%) and diabetes (19.4%) is consistent with other survey data from populations with a comparable age span (14). Our data broadly confirm previous studies showing that low birth weight is associated with a higher prevalence of impaired glucose metabolism (2–10,15–

17), whereas our investigation is based on a substantially larger sample of middle-age and elderly subjects than that of previous studies.

A crucial critique of previous clinical studies that supported the fetal origins hypothesis is that their data have not adequately unadjusted for confounding factors, such as smoking, alcohol consumption, diet, lifestyle, social class, and others (20). In comparison with many other published studies, we had access to data containing more elaborate measures at birth and in adult life. Our data on confounding factors at birth and in adult life cover many different dimensions of socioeconomic status. We found a small attenuation of the effect of birth weight after adjustment for confounding factors at birth and in adult life, thus confirming that the effect of birth weight on glucose tolerance was independent of various other confounding factors. It should be acknowledged that, because of the retrospective nature of the present study, we could not collect information on parental obesity and glucose intolerance, which may affect the glucose metabolism of their offspring and complicate modeling. A future prospective study on this very important issue is highly warranted.

In summary, these data provide the most compelling evidence to date that there is a genuine association between size at birth and risk of impaired glucose homeostasis in Chinese people, after adjustments for various confounding factors in adulthood. Based on present findings, we tentatively conclude that partially established fetal undernutrition may be a risk factor for impaired glucose tolerance or frank type 2 diabetes in adulthood. This risk is independent of those associated with adult obesity, age, smoking, alcohol consumption, and so on. In developing countries such as China, one may hypothesize that improved nutrition in girls and women may offer long-term benefits to their offspring. However, we also conclude that not only should the environment of intrauterine development be emphasized but risk factors in adult lifestyle and behavior should also be highlighted, some of which could be subject to interventions now. Interventions for all of these risk factors could lead to good health at older ages.

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