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Birthweight and adult health outcomes in a biethnic population in the USA

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Summary Recent data indicate that low-birthweight adults are at a higher risk than their high-birthweight peers of developing ischaemic heart disease or a cluster of conditions known as the IRS, which includes dyslipidaemias, hypertension, unfavourable body fat distribution and NIDDM. Thus far these observations have been limited to Caucasians from the United Kingdom. We extended these observations to a broader segment of the general population by studying the association of birthweight and adult health outcomes in a biethnic population of the United States. We divided a group of 564 young adult Mexican-American and non-Hispanic white men and women participants of the San Antonio Heart Study into tertiles of birthweight and compared metabolic, anthropometric, haemodynamic, and demographic characteristics across these tertile categories. Additionally, we studied birthweight as a predictor of the clustering of diseases associated with the IRS, defined as any two or more of the following conditions: hypertension, NIDDM or impaired glucose tolerance, dyslipidaemia. Normotensive, non-diabetic individuals whose birthweight was in the lowest tertile had significantly higher levels of fasting serum insulin and a more truncal fat deposition pattern than individuals whose birthweight was in the highest tertile, independently of sex, ethnicity, and current socioeconomic status. Also, the odds of expressing the IRS increased 1.72 times (95 % confidence interval: 1.16–2.55) for each tertile decrease in birthweight. These findings were independent of sex, ethnicity, and current levels of socioeconomic status or obesity. In conclusion, low birthweight could be a major independent risk factor for the development of adult chronic conditions commonly associated with insulin resistance in the general population. [Diabetologia (1994) 37: 624–631]

Key words Infant, birthweight, insulin resistance, diabetes, truncal obesity, chronic disease.

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Abbreviations: IRS, insulin resistance syndrome; NIDDM, non-insulin dependent diabetes mellitus; HDL, high-density lipoprotein; ANCOVA, analysis of covariance; SES, socioeconomic status; WHR, waist-to-hip circumference ratio; STR, subscapular-to-triceps skinfold ratio; BMI, body mass index; BP, blood pressure; FastI, fasting insulin; 2-h I, 2-h post-load insulin; HDL, high density lipoprotein cholesterol; FastG, fasting glucose; 2-h G, 2-h post-load glucose; Tg, triglycerides; LDL, low density lipoprotein cholesterol; TChol, total cholesterol.

Low birthweight and low weight at 1 year of age have been implicated in the onset of common adult chronic diseases such as ischaemic heart disease [1], hypertension [2], and NIDDM [3]. The mechanisms whereby early development may influence health status in later life are unknown, but the epidemiological evidence is impressive. It has been shown that adults who in early life were exposed to environments characterized by high rates of maternal and neonatal mortality are at a higher risk of dying from cardiovascular disease than adults who were not so exposed [4]. This association appears to be independent of current environmental factors, such as social class, smoking, and alcohol consumption [4]. Moreover, a below-average weight at birth or during early infancy is an independent risk factor for hypertension, glucose intolerance, and cardiovascular disease in middle-age and elderly subjects [5–7]. Similar, but somewhat weaker, effects have been reported among adolescents and young adults [8, 9].

These observations have led Barker and colleagues [3, 4] to hypothesize that "programming", a permanent or long-lasting change caused by subtle stimuli acting early in life on susceptible individuals, is an important contributor to several adult chronic diseases such as dyslipidaemias, high blood pressure, and diabetes. These diseases tend to appear in a cluster which has been labelled syndrome X or the IRS, because chronic insulin resistance is thought to be its underlying metabolic defect [10]. The IRS is commonly, although not necessarily, associated with obesity and particularly with an unfavourable body fat distribution [11].

An important limitation of this programming hypothesis, however, is that thus far the findings have been observed in only one ethnic and nationality group: Caucasians from the United Kingdom. In this report, we attempt to generalize these observations by studying birthweight as a predictor of health status in young adults from San Antonio, Texas, a population composed predominantly of non-Hispanic Caucasians and Mexican-Americans, the latter ethnic group having a high risk for NIDDM [12].

Subjects and methods

This report is based on participants of the San Antonio Heart Study who were born in (or after) 1949, the year in which birthweights were first recorded on birth certificates filed in Bexar County (San Antonio), Texas. The San Antonio Heart Study is a longitudinal population-based study of diabetes and cardiovascular risk factors in 3302 Mexican Americans and 1877 non-Hispanic whites, 25 to 64 years of age, who were enrolled in two phases (1979–1982 and 1984–1988). Detailed descriptions of these surveys have appeared elsewhere [12–14]. Mexican-Americans were defined as individuals whose ancestry and traditions are derived from a Mexican national origin [15].

For each subject, blood specimens were obtained after a 12-h fast and 2 h after the administration of a 75-g oral glucose equivalent load (Glucola; Ames, Elkhart, Ind., USA). Plasma glucose and serum insulin, lipids and lipoproteins were measured using previously described methods [14, 16].

Diabetes mellitus and impaired glucose tolerance were diagnosed according to the criteria of the World Health Organization [17]. Subjects who were being treated with either oral anti-diabetic agents or insulin were also considered to have diabetes regardless of their plasma glucose levels.

Anthropometric measurements (height, weight, and subscapular and triceps skinfolds) were made using standard procedures [18]. Waist circumference was measured at the level of the umbilicus and hip circumference was measured at the level of the greater trochanter. BMI was calculated as weight (in kg) divided by height (in m) squared. The ratio of subscapular-to-triceps skinfold was used as an index of truncal vs peripheral adiposity and the ratio of waist to hip circumference was used as an index of upper body vs lower body adiposity. Systolic and diastolic blood pressures were measured on the right arm of the seated participant using a random zero sphygmomanometer (Hawksley-Gelman, Sussex, UK), after at least a 5-min rest. The blood pressures reported here are the mean of the last two of three readings. Hypertension was defined as a diastolic blood pressure of 95 mm Hg or greater or current use of anti-hypertensive medications [19].

Current socioeconomic status was measured by the Duncan Socioeconomic Index of occupational prestige [20]. Occupations were coded using the scores developed by the Center for Demography and Ecology of the University of Wisconsin at Madison [21]. A high score indicates a high socioeconomic status.

An 8-year follow-up of the cohort enrolled in 1979–1982 has been completed with 80.8 % (n = 1685) of the surviving subjects being re-examined using procedures identical to those used at the baseline examination. A complete description of this follow-up examination has appeared previously [12, 13]. The follow-up of the 1984–1988 cohort is currently in progress and no data from this phase are presented in this paper. In those individuals for whom both baseline and follow-up data were available (n = 100), the more recent data are used in the present analyses.

Of the 5179 participants in the San Antonio Heart Study, 788 stated that they had been born in San Antonio in 1949 or later, and we were able to locate the birth certificates of 582 of these individuals by searching all birth certificates filed with the San Antonio Metropolitan Area Health District from 1949 to 1963. Those whose birth certificate could not be located were perhaps born outside the San Antonio registration area, or their births were not registered, or they misreported their place of birth in the San Antonio Heart Study interviews. Additionally, a group of 18 subjects lacked either metabolic or anthropometric data and were therefore excluded from this report, leaving a final sample size of 564 subjects.

Individuals were considered to have the IRS (syndrome X) if they had two or more of the following conditions: hypertension, diabetes or impaired glucose tolerance, high triglycerides (> 2.8 mmol/l), or low HDL cholesterol (< 0.9 mmol/l in men and < 1.2 mmol/l in women). Prospectively, we have previously described the tendency of these conditions to cluster in individuals with elevated levels of fasting insulin [22].

The study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. All subjects gave informed consent.

Statistical analysis

Fasting insulin, 2-h post-load insulin, and triglycerides showed skewed distributions that were normalized by logarithmic transformation. ANCOVA was used to test for differences between adjusted means. Chi-square and Mantel-Haenszel tests were used to test for associations between discrete variables. Adjusted linear trends were estimated with Pearson or Spearman partial correlation coefficients and adjusted odds ratios were calculated by multiple logistic regression.

As a preliminary step, we tested for secular trends in birthweights during the period covered by this report (1949–1963). In the whole sample, the correlation coefficient (r, Spearman) between birthweight and year of birth was –0.047 (p = 0.250). In Mexican Americans the coefficients were 0.021 (p = 0.768) in men and –0.040 (p = 0.540) in women. In non-Hispanic whites the coefficients were –0.207 (p = 0.088) in men and –0.202 (p = 0.106) in women. The downward secular trend in birthweights may be due to advances in neonatal care allowing survival of smaller babies. We elected to adjust for age at the time of examination, rather than year of birth, to control for both secular trends in birthweight and age effects on anthropometric, haemodynamic, and metabolic variables. The Spear-

Table 1. Characteristics of the study population, by sex and ethnicity

	Men		Women		p value	
	Mexican American	Non-Hispanic whites	Mexican American	Non-Hispanic whites	Sex	Ethnicity
n	185	66	228	62		
Birthweight (kg)	3.40	3.46	3.23	3.33	< 0.001	0.097
Age (years)	30.9	32.1	31.7	32.2	0.034	0.022
SES (Duncan)	47.7	55.5	44.5	58.3	0.320	< 0.001
WHR	0.91	0.92	0.82	0.79	(a)	(a)
STR	1.68	1.44	1.19	0.96	< 0.001	< 0.001
BMI (kg/m²)	28.3	26.2	27.8	24.9	0.172	< 0.001
Systolic BP (mmHg)	119.6	117.5	109.5	108.6	< 0.001	0.162
Diastolic BP (mmHg)	72.8	72.4	68.2	68.0	< 0.001	0.744
FastI (pmol/l)	65.0	57.4	57.1	42.2	0.020	0.014
2-h I (pmol/l)	293.4	195.8	417.5	280.9	< 0.001	< 0.001
HDL (mmol/l)	1.11	1.12	1.24	1.30	< 0.001	0.339
FastG (mmol/l)	4.78	4.74	4.54	4.40	< 0.001	0.083
2-h G (mmol/l)	5.10	4.95	5.63	5.21	< 0.001	0.060
Tg (mmol/l)	1.41	1.23	1.09	0.94	< 0.001	0.014
LDL (mmol/l)	3.23	3.02	2.84	2.90	< 0.001	0.332
TChol (mmol/l)	5.06	4.77	4.64	4.67	< 0.001	0.154

(a) The interaction between sex and ethnicity is significant (p = 0.007). The p value for the ethnic difference among men is 0.350, and among women is 0.001

man correlation coefficient between age at examination and year of birth was high (–0.85, $p < 0.001$), but less than 1.0, since subjects born in the same year might have been examined in different years, thus giving them slightly different study ages. All statistical analyses were performed using programs from the SAS Institute [23].

Results

The results are reported in two parts: in the first part (Tables 1–4) we have excluded nine NIDDM and 14 hypertensive subjects to search for associations between birthweight and several current demographic, anthropometric and metabolic variables in normotensive, non-diabetic subjects (n = 541). The second part of the results includes the entire sample (n = 564) and explores the association between birthweight and the IRS (syndrome X), as defined above.

Table 1 shows the means by sex and ethnicity of demographic, anthropometric, metabolic, and physiologic variables in 541 normotensive and non-diabetic subjects. On average, the birthweight of Mexican-Americans is about 100 g less than that of non-Hispanic whites and the birthweight of women is about 200 g less than that of men, although only the latter difference was statistically significant. Most of the other variables in this study also show significant sex differences, the only exceptions being BMI and socioeconomic status. Mexican-Americans are significantly younger and are of lower socioeconomic status than non-Hispanic whites. Also, Mexican-Americans are more obese and have a more truncal fat distribution than non-Hispanic whites. Mexican-American women have significantly higher waist-to-hip circumference ratios than non-Hispanic white women, but this ethnic difference is not seen in men. Metabolically, Mexican-Americans show higher values of fasting and 2-h post-load insulin concentrations, and plasma triglycerides than non-Hispanic whites. Additionally, fasting glucose and 2-h post-load glucose tend to be higher in Mexican-Americans, although these differences are not statistically significant.

Since Mexican Americans had slightly (although not statistically significantly) lower birthweights than non-Hispanic whites, and also tended to have worse metabolic profiles, it became essential to adjust for ethnicity in the analyses of the effect of birthweight on current metabolic variables. This adjustment was done both by analysing the two ethnic groups separately and by adjusting for ethnicity in pooled analyses. We also tested for ethnicity-birthweight interactions in the pooled analyses, but these were invariably statistically insignificant. Their p values ranged from 0.094 for total cholesterol to 0.991 for the waist-to-hip circumference ratio.

Tables 2 (women) and 3 (men) show the age-adjusted means of the variables presented in Table 1 by tertile of birthweight and by ethnic group. In Mexican-American women, birthweight is significantly and inversely associated with the subscapular-to-triceps skinfold ratio, systolic blood pressure, diastolic blood pressure, fasting insulin, and fasting glucose. Two-hour post-load insulin shows a similar inverse trend with birthweight in this group, although this trend is not statistically significant. This group also shows a statistically significant direct association between birthweight and current socioeconomic status. In non-Hispanic white women (Table 2) none of the associations between birthweight and the variables studied reached statistical significance. How-

Table 2. Age-adjusted mean values of selected variables by ethnicity and tertile of birthweight in women

	Tertile of birthweight for:							
	Mexican Americans				Non-Hispanic whites			
	1	2	3		1	2	3	
n	78	74	76		20	22	20	
Birthweight (kg)	2.68	3.26	3.77		2.74	3.39	3.86	
				p value				*p* value
SES (Duncan)	40.7	44.3	48.7	0.050	57.9	59.2	57.7	0.953
WHR	0.83	0.81	0.82	0.312	0.80	0.79	0.77	0.353
STR	1.34	1.11	1.12	0.025	1.05	0.96	0.87	0.279
BMI (kg/m^2)	28.7	27.7	27.0	0.238	25.3	24.8	24.6	0.943
Systolic BP (mmHg)	111.2	110.7	106.6	0.020	111.5	107.4	107.0	0.424
Diastolic BP (mmHg)	70.0	67.9	66.7	0.033	69.2	68.0	66.9	0.649
FastI (pmol/l)	74.2	54.3	45.7	0.001	50.4	44.6	32.9	0.377
2-h I (pmol/l)	478.4	407.3	372.2	0.184	273.4	350.1	228.7	0.245
HDL	1.22	1.26	1.25	0.711	1.39	1.24	1.26	0.371
FastG (mmol/l)	4.57	4.62	4.43	0.040	4.36	4.24	4.62	0.076
2-h G (mmol/l)	5.74	5.62	5.52	0.696	5.37	5.09	5.19	0.839
Tg (mmol/l)	1.16	1.05	1.05	0.337	0.94	0.89	1.00	0.767
LDL (mmol/l)	2.79	2.87	2.87	0.795	3.04	2.94	2.70	0.446
TChol (mmol/l)	4.61	4.68	4.65	0.881	4.90	4.64	4.48	0.363

Table 3. Age-adjusted mean values of selected variables by ethnicity and tertile of birthweight in men

	Tertile of birthweight for:							
	Mexican Americans				Non-Hispanic whites			
	1	2	3		1	2	3	
n	61	62	62		22	22	22	
Birthweight (kg)	2.88	3.40	3.90		2.96	3.50	3.94	
				p value				*p* value
SES (Duncan)	42.9	47.3	52.7	0.027	54.0	53.7	58.6	0.496
WHR	0.91	0.91	0.92	0.958	0.91	0.92	0.92	0.877
STR	1.74	1.65	1.66	0.570	1.54	1.39	1.41	0.461
BMI (kg/m^2)	28.0	28.1	28.6	0.760	25.0	26.9	26.7	0.368
Systolic BP (mmHg)	120.5	119.4	119.1	0.701	120.5	118.1	113.8	0.093
Diastolic BP (mmHg)	73.5	72.7	72.2	0.750	73.5	72.6	71.2	0.468
FastI (pmol/l)	64.3	64.5	66.4	0.973	70.6	59.9	44.0	0.213
2-h I (pmol/l)	330.2	300.04	255.9	0.505	207.9	196.9	184.1	0.944
HDL (mmol/l)	1.09	1.16	1.09	0.270	1.09	1.09	1.17	0.724
FastG (mmol/l)	4.77	4.77	4.79	0.974	4.86	4.77	4.58	0.188
2-h G (mmol/l)	5.06	5.16	5.08	0.920	4.86	5.19	4.78	0.562
Tg (mmol/l)	1.47	1.31	1.45	0.536	1.55	1.28	0.95	0.025
LDL (mmol/l)	3.24	3.19	3.27	0.881	3.03	2.85	3.18	0.465
TChol (mmol/l)	5.07	5.02	5.10	0.886	4.86	4.61	4.85	0.639

ever, the subscapular-to-triceps skinfold ratio and fasting insulin tend to show the same inverse trend with birthweight observed in Mexican-American women.

In Table 3, the birthweight of Mexican-American men does not show significant associations with any of the anthropometric or metabolic variables, although the trend in 2-h insulin levels is similar to that in Mexican-American women and, also as in Mexican-American women, socioeconomic status shows a statistically significant positive association with birthweight. Among the non-Hispanic white men (Table 3) only plasma triglycerides show a statistically significant inverse relationship with birthweight. Systolic and diastolic blood pressures, fasting and 2-h insulin, and fasting glucose also show inverse trends with birthweight, but these are not statistically significant. Since the failure of many of the anticipated trends in Tables 2 and 3 to achieve statistical significance may have resulted from small sample size, we analysed the pooled data by tertiles of birthweight, adjusting for age, sex, and ethnic group (Table 4).

Table 4 shows that women and Mexican-Americans are over-represented in the lowest tertile and under-represented in the upper tertile of birthweight, but only the proportion of women is significantly different across these tertiles. The lower part of Table 4 presents the mean values across tertiles of birthweight of the anthropometric and metabolic variables after adjusting

Table 4. Mean values of selected variables by birthweight tertile. The ANCOVA and the correlations (trend) were performed adjusting for age, sex, and ethnicity

	Birthweight tertile				
	1	2	3		
n	178	181	182		
Birthweight (kg)	2.78	3.35	3.85		
range	(1.67–3.17)	(3.18–3.55)	(3.56–5.11)		
Age (years)	31.4	31.5	31.7	*p* value chi-square	
% Women	64.0	51.9	45.1	0.001	
% Mexican American	79.8	78.5	70.9	0.099	
				p value	
				ANCOVA	Trend
SES (Duncan)	45.4	49.1	51.0	0.026	0.043
WHR	0.86	0.86	0.86	0.596	0.128
STR	1.46	1.36	1.28	0.006	0.003
BMI (kg/m^2)	27.6	27.3	27.4	0.863	0.072
Systolic BP (mmHg)	114.8	114.3	112.4	0.077	0.010
Diastolic BP (mmHg)	71.0	70.5	69.3	0.148	0.005
FastI (pmol/l)	67.0	57.4	49.8	0.005	0.001
2-h I (pmol/l)	355.9	351.4	282.6	0.055	0.018
HDL (mmol/l)	1.18	1.19	1.19	0.959	0.631
Fastg (mmol/l)	4.68	4.58	4.63	0.189	0.065
2-h G (mmol/l)	5.40	5.29	5.26	0.622	0.125
Tg (mmol/l)	1.26	1.15	1.15	0.187	0.065
LDL (mmol/l)	2.96	2.99	3.01	0.984	0.912
TChol (mmol/l)	4.85	4.76	4.80	0.750	0.700

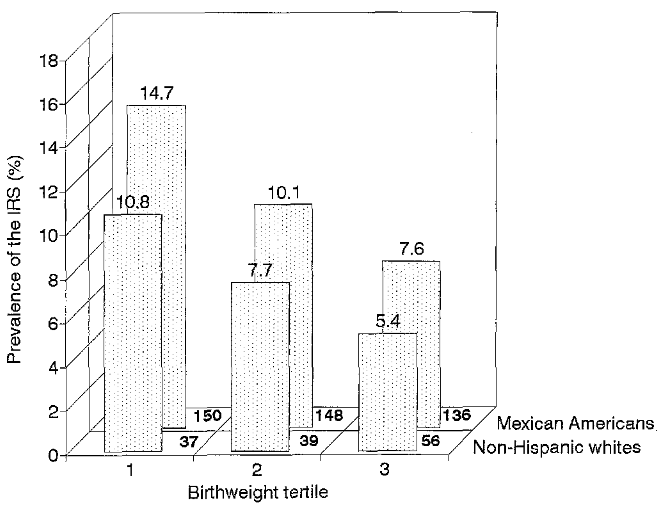

Fig. 1. Prevalence of the IRS by ethnicity and tertiles of birthweight in 562 subjects from the San Antonio Heart Study. The number at the base of each column is the number of subjects in that category

for age, sex, and ethnicity. In addition to the *p* value for the ANCOVA, Table 4 also includes a test for linear trend (Pearson correlations), to see if the continuous increase (or decrease) of a given variable follows a significant linear association with birthweight. Table 4 shows that, after adjusting for age, sex, and ethnicity the statistically significant differences in current socioeconomic status across tertiles of birthweight persist; on average, the subjects in the lowest tertile of birthweight have a lower current socioeconomic status than those in the two upper tertiles. The linearity of this association is also statistically significant. Additionally, the subscapular-to-triceps skinfold ratio declines significantly with birthweight tertiles and its linear association with birthweight is also statistically significant. Those subjects with low birthweight have statistically significantly more truncal fat deposition than subjects with high birthweight. Interestingly, however, there is no trend across birthweight tertiles for upper vs lower body adiposity as assessed by waist-hip ratio. Low-birthweight subjects show higher systolic and diastolic blood pressures than high-birthweight subjects, although only the linear trend is statistically significant for these variables.

Among the metabolic variables (Table 4), only fasting insulin declines across tertiles of birthweight with both linear trend and *F*-statistic (ANCOVA) statistically significant: subjects in the lower birthweight tertile have significantly more elevated fasting insulin levels than subjects in the upper tertile. Two-hour post-load fasting insulin also decreases with increasing birthweight, but only its linear association with birthweight is statistically significant. Fasting glucose and triglycerides show weak linear trends with birthweight which statistically, however, are not significant. Further adjustment for socioeconomic status did not change these associations (results not shown).

The results presented above were obtained among normoglycaemic and normotensive subjects. In the fol-

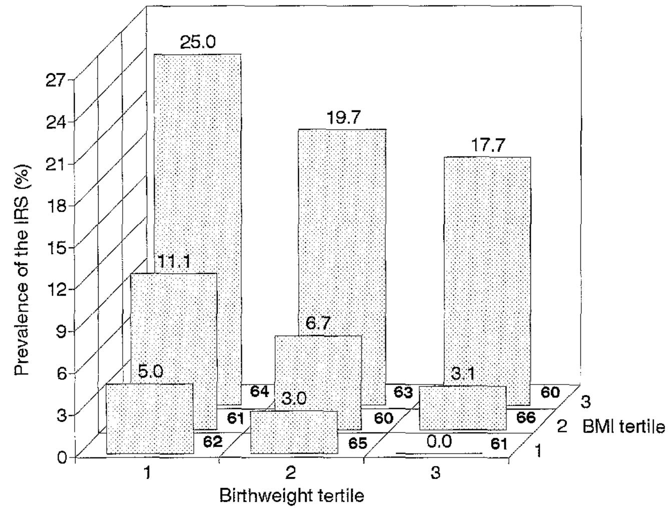

Fig. 2. Prevalence of the IRS by tertiles of birthweight and BMI in 562 subjects from the San Antonio Heart Study. The number at the base of each column indicates the number of subjects in that category. The first tertile of BMI has a mean of 21.8 kg/m^2 (range: 17.2–24.5); the second has a mean of 26.9 (range: 24.5–29.2), and the third has a mean of 34.3 (range: 29.4–52.4). The mean and range for each tertile of birthweight are given in Table 4

lowing analyses, we include the NIDDM (n = 9) and the hypertensive (n = 14) subjects to search for associations between birthweight and the clustering of traits of the IRS as defined above.

The status of the IRS could be ascertained in 562 subjects, 10.1 % (57 of 562) of whom were found to have this syndrome. Among men, the percentages were 11.9 (23 of 193) in Mexican-Americans and 7.3 (5 of 69) in non-Hispanic whites. Among women, the percentages were 10.1 (24 of 237) in Mexican-Americans and 7.9 (5 of 63) among non-Hispanic whites. Figure 1 shows similar strong inverse associations between birthweight and the prevalence of IRS conditions in the two ethnic groups. Given this similarity, we pooled the 562 subjects to study the association between birthweight and the IRS.

Since obesity is closely associated with the IRS, we adjusted for obesity by dividing our sample into tertiles of BMI, in addition to the division by tertiles of birthweight.

Figure 2 shows the percent of subjects manifesting two or more IRS-related disorders within each BMI-birthweight tertile category. In the lowest tertile of birthweight and highest tertile of BMI, 16 out of 64 subjects (25 %) manifest two or more disorders related with the IRS. By contrast, none of the 61 subjects in the highest tertile of birthweight and lowest tertile of BMI manifest IRS related disorders. The frequencies of the IRS in the other tertiles of birthweight and BMI are intermediate between these two extremes with the following characteristics: the increasing number of subjects with IRS across rising BMI tertiles has a statistically significant trend (chi-square = 31.92, 1 df, $p < 0.001$); similarly, the decreasing number of subjects with IRS across rising birthweight tertiles also has a statistically significant trend (chi-square = 4.74, 1 df, $p = 0.030$).

Using multiple logistic regression to adjust for sex, ethnicity, age, socioeconomic status, and birthweight (continuous), the adjusted odds of expressing the IRS increase by a factor of 2.86 (95 % confidence interval: 1.74, 4.71) with increasing tertile of BMI. On the other hand, after adjusting for sex, ethnicity, age, socioeconomic status, and BMI (continuous), the odds of expressing the IRS increase by a factor of 1.72 (95 % confidence interval: 1.16, 2.55) with decreasing tertile of birthweight. Further adjustment for the subscapular-to-triceps skinfold ratio or waist-hip ratio does not appreciably affect these odds ratios.

Discussion

We have shown that in normotensive and non-diabetic young adults, birthweight is significantly inversely associated with fasting serum insulin concentrations and with truncal fat deposition. Systolic and diastolic blood pressures, and 2-h post load insulin also tend to decrease, although perhaps less consistently, with increasing birthweight. These associations are independent of confounding variables such as sex, ethnicity, and current socioeconomic status. Furthermore, we have shown that insulin resistance (as assessed by fasting insulin levels) tracks the distribution of the IRS traits across the BMI-birthweight tertile categories.

Thus, this report supports the programming hypothesis of Barker and colleagues [3, 4] and extends it to a broader segment of the general population. The strength of the associations is highlighted by the fact that they were observed despite two methodological limitations: 1) this study was restricted to young adults, among whom chronic diseases are still relatively infrequent; 2) we used fasting insulin as a crude proxy for insulin resistance. On the other hand, reports from the San Antonio Heart Study and other populations have shown that high levels of fasting insulin are associated with (or predict) NIDDM [13, 16, 24, 25], an unfavourable fat distribution [26], worse serum lipid profiles [27–29], essential hypertension [30, 31] and, in particular, the clustering of disorders commonly related to insulin resistance [22, 32].

Our results, obtained from young adults, point to insulin resistance and truncal fat deposition, as indicated by the subscapular-to-triceps skinfold ratio, accompanied by rising trends of systolic and diastolic blood pressures, as among the earliest manifestations of the unfavourable effects of low birthweight on adult health outcomes. Noticeably, the indicator of upper body adiposity, waist-hip ratio, which has been strongly implicated in the IRS [11], failed to show association with birthweight in this group of young adults. We have no explanation for this, but we have previously shown that these two indices may indicate different aspects of body fat distribution [33]. Our results also indicate that the transition from a low birthweight newborn to an obese adult is associated with the worst and the transition from a high birthweight newborn to a lean adult with the best metabolic outcomes.

This report together with previous studies [3, 7] support a mostly environmental explanation for the surge of insulin resistant conditions with industrialization: in historically deprived populations suddenly exposed to affluent environments, the transitions from low-birthweight newborns to obese adults, i. e. the pattern associated with the worst metabolic consequences, would presumably be very common. This explanation expands on the thrifty genotype hypothesis [34, 35], which attributes the surge of NIDDM in traditional populations undergoing modernization to a genotype-by-environment interaction. Interestingly, and unlike the thrifty genotype hypothesis, the programming hypothesis also provides a plausible explanation for the rapid decline of these conditions with time, i. e. a stable affluence is associated with healthier mother-child environments, which may make the transition from high-birthweight newborns to lean adults more likely. Unfortunately, a stable affluence is usually accompanied by a more sedentary lifestyle, which makes obesity more common and may offset some of the benefits of a healthy fetal development.

The thrifty genotype hypothesis emphasizes the important role that genes, guided by natural selection, may have played in the recent surge of some chronic metabolic diseases now considered epidemic in many aboriginal populations and those genetically related to them [36, 37]. Today, the search for these genes is the subject of intense scientific research and has had some success [38]. Equally clear, however, is the fact that there must be some powerful environmental factors involved in these chronic disease epidemics, because the time frame of these epidemics is too short for natural selection to have acted. The challenge, then, has been to identify these environmental factors. Besides dietary changes and sedentary lifestyles [39] that ultimately lead to obesity, only minor factors have been identified. Here we report what we believe to be another major risk factor for chronic disease: having a low birthweight probably as a result of having been exposed to an unfavourable mother-child environment. For each one tertile decrease in birthweight, a decrease of 535 g on average, the odds of developing conditions related to insulin resistance increase by 72 %.

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