Birth Weight, Adult Weight, and Girth as Predictors of the Metabolic Syndrome in Postmenopausal Women

The Rancho Bernardo Study

DONALD E. YARBROUGH, BS
ELIZABETH BARRETT-CONNOR, MD
DONNA KRITZ-SILVERSTEIN, PHD
DEBORAH L. WINGARD, PHD

OBJECTIVE — Recent studies have demonstrated an association between low birth weight and chronic and metabolic disorders in adulthood such as type 2 diabetes, hypertension, and dyslipidemia. These disorders tend to cluster in a condition known as the metabolic syndrome (syndrome X). Only two studies have reported an association of birth weight to the metabolic syndrome. The present study is distinguished as the only study to focus on postmenopausal women.

RESEARCH DESIGN AND METHODS — Subjects were 303 community-dwelling, postmenopausal Caucasian women aged 50–84 years. Metabolic and anthropometric variables were measured at a clinic visit; birth weight was assessed by self-report on a mailed questionnaire.

RESULTS — The metabolic syndrome, defined as the simultaneous presence of hypertension, dyslipidemia, and abnormal glucose tolerance, was present in 7.9% of these women. Compared with women in the highest birth weight tertile (8.1–13.0 lb, mean 9.4 lb), those in the lowest birth weight tertile (2.5–6.8 lb, mean 5.5 lb) exhibited an increased prevalence (12.0 vs. 4.3%, $P < 0.05$) and 2.41 times the risk (95% CI 1.06–5.51) of developing the metabolic syndrome. Women with a heavy birth weight had an increased risk of adult obesity. Nevertheless, women in the lowest birth weight tertile who became adults in the highest tertile of BMI (>25.2 kg/m^2) or waist circumference (>80.7 cm) had the highest prevalence of the metabolic syndrome (~30%).

CONCLUSIONS — Low birth weight coupled with adult obesity is a strong determinant of the metabolic syndrome in postmenopausal women.

Diabetes Care 21:1652–1658, 1998

Certain chronic and metabolic disorders (hypertension, glucose intolerance, central obesity, dyslipidemia) tend to cluster in the same individuals leading to an increase in mortality from cardiovascular disease (1). This syndrome has been labeled by several names, depending on which factors are included in the definition and the proposed underlying mechanism. Commonly used descriptions include syndrome X (2), the deadly quartet (3), the atherothrombogenic syndrome (4), and the insulin resistance syndrome (5). The term "metabolic syndrome" will be used in this study, highlighting the simultaneous presence of three or more metabolic conditions while avoiding confusion with the term "syndrome X" of microvascular angina (6) and assumptions about the underlying mechanisms (7). There is no universally accepted definition for the metabolic syndrome. Different authors have included numerous conditions in the syndrome, such as hyperuricemia, short stature, hyperinsulinemia, and increased clotting factors. Most lists include hypertension, glycemia or type 2 diabetes, and dyslipidemia; these conditions are the focus of this report.

Several investigators using different populations have reported an association of low birth weight with an increased risk of some components of the metabolic syndrome and cardiovascular disease. Studies conducted in the U.K. (8,9), Sweden (10,11), South India (12), and the U.S. (13–15) have focused primarily on adult men. The purpose of the present study was to examine the relation of birth weight to the metabolic syndrome and its components among a population-based sample of older women.

RESEARCH DESIGN AND METHODS

Overview of study design

Between 1972 and 1974, 82% of all residents from a middle to upper-middle class, Caucasian, Southern California community (Rancho Bernardo) were surveyed for the prevalence of heart disease risk factors as part of the Lipid Research Clinic Prevalence Study. These individuals have been followed with yearly mailed questionnaires and periodic clinic evaluations. Between 1984 and 1987, 78% (n = 1,525) of all surviving women aged ≥40 years at enrollment participated in a follow-up clinic visit that focused on diabetes (16); at this visit, metabolic syndrome and anthropometric variables were measured. In 1991, a mailed questionnaire asked participants to indicate their birth weight and the source of their information (birth certificate, family bible, baby book, parent). Of the 1,252 women who participated in the 1984–1987 visit and responded to the questionnaire, the

From the Department of Family and Preventive Medicine (D.E.Y., E.B.-C., D.K.-S., D.L.W.), University of California, San Diego, California; and the University of Alabama School of Medicine (D.E.Y.), Birmingham, Alabama.

Address correspondence and reprint requests to Elizabeth Barrett-Connor, MD, Department of Family and Preventive Medicine, University of California, San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0607.

Received for publication 17 February 1998 and accepted in revised form 22 June 1998.

Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; SES, socioeconomic status.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Age-adjusted mean and distribution of metabolic and anthropometric variables by birth weight tertiles*

	Mean ± SD	Birth weight tertile			*P* value
		Low ($n = 92$)	Middle ($n = 112$)	High ($n = 99$)	
Metabolic variables					
Systolic blood pressure (mmHg)	134.4 ± 20.6	136.8	130.7	135.9	NS
Diastolic blood pressure (mmHg)	74.6 ± 8.7	75.3	73.7	74.9	NS
Triglycerides (mmol/l)	1.1 ± 0.02	1.1	1.1	1.1	NS
HDL cholesterol (mmol/l)	1.8 ± 0.4	1.8	1.8	1.9	NS
Fasting plasma glucose (mmol/l)	5.4 ± 0.7	5.5	5.4	5.2	0.01
Postchallenge plasma glucose (mmol/l)	7.4 ± 2.6	7.8	7.7	6.8	0.01
Anthropometric variables					
BMI (kg/m^2)	24.3 ± 3.8	23.8	24.3	24.7	NS
Waist circumference (cm)	77.5 ± 9.1	76.1	77.0	79.4	0.03
Waist-to-hip ratio (cm/cm × 100)	78.0 ± 6.1	78.0	77.0	79.0	NS
Current weight (lb)	138.7 ± 23.3	132.6	138.8	144.1	<0.01
Maximum lifetime weight (lb)	145.7 ± 23.5	139.2	145.0	152.4	<0.01

A total of 303 women aged 50–84 years participated from Rancho Bernardo, CA, 1984–1987. NS, $P > 0.10$.

303 (24.2%) who were aged ≥50 years, postmenopausal, and able to provide birth weight data are the focus of this report.

Measurements

At the 1984–1987 clinic visit, a standardized interview was used to obtain information concerning physician-diagnosed diabetes, family history of diabetes, maximum (nonpregnant) lifetime weight, and lifestyle factors such as cigarette smoking, alcohol consumption, and physical activity. Current use of medications for hypertension, diabetes, or estrogen-replacement therapy was confirmed by examination of prescriptions or pill containers brought to the clinic for that purpose. After the woman had been seated quietly for 5 min, two blood pressure readings were recorded at least 30 s apart using a mercury sphygmomanometer, according to the Hypertension Detection and Follow-up Program (HDFP) protocol (17). The mean of the two readings was used in the present analysis. Height, weight, and waist and hip circumference were measured in the clinic with the participant wearing light clothing and no shoes. BMI (kilograms per meter squared) and waist-to-hip ratio (waist circumference in centimeters per hip circumference in centimeters times 100) were calculated. A 75-g oral glucose tolerance test was administered between 7:00 and 11:00 A.M., after a 12- to 16-h fast. Blood was obtained by venipuncture before and 2 h after glucose load.

Glucose was measured by the glucose-oxidase method. Fasting plasma lipids and lipoproteins were measured in a Lipid Research Clinic Laboratory under continuous standardization by the Centers for Disease Control, Atlanta, GA. Total cholesterol and triglyceride levels were measured by enzymatic techniques with an ABA-200 biochromatic analyzer (Abbott Laboratories, Irving, TX), a high performance cholesterol reagent (number 236691, Boehringer-Mannheim Diagnostics, Indianapolis, IN), and a triglyceride agent (number 6097, Abbott Laboratories). HDL cholesterol was measured by precipitating the other lipoproteins with heparin and manganese chloride according to the standardized procedures of the Lipid Research Clinics Manual (18). LDL cholesterol was calculated using the Friedewald formula (19).

Definitions and categorical cut points

Type 2 diabetes was defined by a fasting plasma glucose level ≥7.0 mmol/l (126 mg/dl) or a 2-h postchallenge glucose level ≥11.1 mmol/l (200 mg/dl), a previous physician diagnosis of type 2 diabetes, or use of antidiabetic medication, reflecting the recent 1998 guidelines from the American Diabetes Association (20). Women with a fasting plasma glucose level between 6.1 and 7.0 mmol/l (110–126 mg/dl) were considered to have impaired fasting glucose (IFG), and those with a 2-h postchallenge glucose level between 7.8 and 11.1 mmol/l (140–200 mg/dl) were considered to have impaired glucose tolerance (IGT). Women with either IFG, IGT, or type 2 diabetes were considered to have abnormal glucose tolerance.

Hypertension was defined by an average measured systolic blood pressure ≥160 mmHg or a diastolic blood pressure ≥90 mmHg, a previous diagnosis of hypertension by a physician, or the use of antihypertensive medications. Dyslipidemia was defined as fasting plasma triglycerides ≥2.3 mmol/l (200 mg/dl) or HDL cholesterol levels ≤1.4 mmol/l (55 mg/dl). The metabolic syndrome was defined as the simultaneous presence of abnormal glucose tolerance, hypertension, and dyslipidemia.

Anthropometric variables were categorized as high by the following cut points: BMI ≥26 kg/m^2, waist circumference ≥80 cm, waist-to-hip ratio ≥85 cm/cm × 100, current weight ≥134.9 lb (median split of sample), and maximum lifetime (nonpregnant) weight ≥142.0 lb (median split of sample). Upper tertiles of the sample were similar to standard cut points (BMI >25.2 kg/m^2 and waist circumference >80.7 cm).

Among these women aged ≥50 years, postmenopause was defined by having had a hysterectomy or not currently having menstrual periods.

Statistical analysis

To adjust for skewness in triglyceride values, analyses were performed on log-transformed values with antilogs presented. Means for each continuous outcome and frequency distribution for categorical outcomes were calculated. Age-adjusted comparisons by tertile of birth weight were performed with analysis of covariance (ANCOVA) for continuous variables and with the Mantel-Haenszel Extension Test for categorical variables. Hierarchical multiple regression analysis for continuous outcomes and logistic regression analysis for

Table 2—*Age-adjusted categorical comparisons of metabolic and anthropometric variables by birth weight tertiles*

	% Total	Birth weight tertile			*P* value
		Low (*n* = 92)	Middle (*n* = 112)	High (*n* = 99)	
Metabolic variables					
Systolic blood pressure (≥160 mmHg)	11.2	15.7	9.5	11.3	NS
Diastolic blood pressure (≥90 mmHg)	4.3	6.5	5.8	4.3	NS
Triglycerides (≥2.3 mmol/l)	9.9	13.2	11.1	8.8	NS
HDL cholesterol (≤1.4 mmol/l)	24.4	36.8	23.5	15.1	<0.01
Fasting plasma glucose (≥6.1 mmol/l)	10.6	15.6	9.4	9.4	NS
Postchallenge plasma glucose (≥7.4 mmol/l)	35.0	34.8	35.5	32.5	NS
Anthropometric variables					
BMI (≥26 kg/m^2)	27.4	27.1	28.9	31.0	NS
Waist circumference (≥80 cm)	35.6	29.1	32.3	45.2	<0.05
Waist-to-hip ratio (≥85 cm/cm × 100)	11.2	14.3	9.0	13.3	NS
Current weight (≥134.9 lb)	49.8	35.3	38.9	41.6	<0.01
Maximum lifetime weight (≥142.0 lb)	51.5	43.9	47.3	63.0	<0.01

A total of 303 women aged 50–84 years participated from Rancho Bernardo, CA, 1984–1987. Categorical cut points were established using clinical criteria for all variables except current weight and maximum lifetime weight, which were based on a median split of the sample. NS, $P > 0.10$.

categorical outcomes were used to examine the independent relation of birth weight tertiles to the metabolic syndrome and its components after adjustment for the potentially confounding covariates of age and obesity. All statistical tests were two-tailed.

RESULTS — Among the 303 women aged 50–84 (67.1 ± 8.7 [mean ± SD]) years, birth weight ranged from 2.5 to 13.0 (7.5 ± 1.8) lb. In the lowest tertile, the average birth weight was 5.5 lb (range 2.5–6.8), in the middle tertile 7.5 lb (range 6.9–8.0), and in the highest tertile 9.4 lb (range 8.1–13.0). Overall, 35% of the women reported current estrogen use, 14% current smoking, 84% exercising three or more times a week, and 23% a positive family history of diabetes. Among the 68% who were drinkers, the average amount of alcohol consumed the previous week was 77.4 ± 106.3 ml. Because these potential confounders did not differ by birth weight (data not shown), analyses were not adjusted for these variables.

Table 1 shows metabolic and anthropometric variables by tertile of birth weight. Table 2 presents age-adjusted categorical comparisons of metabolic and anthropometric variables by birth weight tertiles. Categorical cut points were chosen a priori based on clinical criteria, except for current weight and maximum weight, which were divided by a median split. Tables 3 and 4 present regression analyses of metabolic syndrome variables in the lowest versus highest birth weight tertile after adjusting for age and either BMI or waist circumference. β weights for continuous dependent variables are presented in Table 3, and odds ratios for categorical variables (defined by the same cut points used in Table 2) are presented in Table 4.

As shown in Table 5, dyslipidemia was prevalent in 29% of the women, and women in the lowest tertile of birth weight were 1.76 times more likely to develop dyslipidemia than women in the highest tertile. Abnormal glucose tolerance was present in 39% of the women but did not differ significantly by birth weight tertile, while the age-adjusted prevalence of type 2 diabetes decreased incrementally from the lowest to the highest birth weight tertile, with rates of 16.3, 13.3, and 10.7%, respectively ($P > 0.05$). The overall prevalence of hypertension was 42% and did not vary by birth weight; exclusion of women taking antihypertensives (26.1%) did not change the results (data not shown). Although glucose intolerance and hypertension were not individually associated with birth weight, these variables contributed to the association with the metabolic syndrome. Women in the lowest tertile of birth weight had nearly 2.5 times the odds of having the metabolic syndrome when compared with the highest birth weight tertile, and this risk increased after adjustment for obesity. Of the women, 35% were currently using estrogen; exclusion

Table 3—*Age- and obesity-adjusted multiple regression analyses comparing the lowest to the highest birth weight tertile on metabolic factors as continuous variables*

	β weight	*P* value
Adjusted for BMI		
Systolic blood pressure	1.41	NS
Diastolic blood pressure	0.11	NS
Triglycerides	−0.012	0.07
HDL cholesterol	0.065	0.07
Fasting plasma glucose	−0.20	0.001
Postchallenge plasma glucose	−0.73	0.001
Adjusted for waist circumference		
Systolic blood pressure	1.27	NS
Diastolic blood pressure	−0.03	NS
Triglycerides	−0.012	0.01
HDL cholesterol	0.083	0.02
Fasting plasma glucose	−0.21	0.001
Postchallenge plasma glucose	−0.78	0.001

A total of 303 women aged 50–84 years participated from Rancho Bernardo, CA, 1984–1987. NS, $P > 0.10$.

Table 4—*Age- and obesity-adjusted logistic regression analyses comparing the lowest to the highest birth weight tertile on metabolic factors as categorical variables*

	OR (95% CI)
Adjusted for BMI*	
Systolic blood pressure	1.00 (0.59–1.71)
Diastolic blood pressure	2.02 (0.72–5.69)
Triglycerides	2.04 (1.04–4.00)
HDL cholesterol	1.96 (1.26–3.05)
Fasting plasma glucose	0.69 (0.39–1.23)
Postchallenge plasma glucose	0.85 (0.63–1.15)
Adjusted for waist circumference*	
Systolic blood pressure	0.94 (0.54–1.61)
Diastolic blood pressure	2.05 (0.73–5.75)
Triglycerides	2.37 (1.19–4.73)
HDL cholesterol	2.29 (1.43–3.65)
Fasting plasma glucose	0.64 (0.36–1.15)
Postchallenge plasma glucose	0.84 (0.59–1.19)

A total of 303 women aged 50–84 years participated from Rancho Bernardo, CA, 1984–1987. NS, $P > 0.10$. *Categorical dependent variables are defined in Table 2.

of these women did not materially change the results (data not shown).

Figures 1 and 2 show the prevalence of the metabolic syndrome by tertile of birth weight and by tertile of adult BMI or waist circumference, respectively. Women in the lowest tertile of birth weight and the highest tertile of adult obesity (BMI >25.2 kg/m^2) or central adiposity (waist circumference >80.7 cm) had the highest prevalence of the metabolic syndrome (~30%), while none of the women in the highest tertile of birth weight and the lowest tertile of adult obesity had the metabolic syndrome. Testing for formal interactions revealed a significant difference between the prevalence of metabolic syndrome only in the highest tertile of adult obesity ($P < 0.01$). Analysis by tertile of current weight and maximum lifetime weight yielded similar results, but there was no association of birth weight with tertile of waist-to-hip ratio (data not shown).

Many of the women in the Rancho Bernardo Study were born at home before birth certificates were formally issued, and only 24.2% of age-eligible women knew their birth weight (53% from a parent and 47% from other sources such as birth certificates and baby books). Among all women who returned the mailed survey, those who reported a birth weight were significantly younger (67.1 vs. 71.2 years, $P < 0.01$) and had lower age-adjusted diastolic blood pressure (74 vs. 76 mmHg, $P = 0.05$) and waist-to-hip ratio (79 vs. 80 cm/cm × 100, $P = 0.001$) than women who did not report a birth weight. They did not differ with regard to any of the other variables measured.

CONCLUSIONS — The metabolic syndrome, characterized by the cluster of abnormal glucose tolerance, hypertension, and dyslipidemia, was present in 7.9% of these community-dwelling Caucasian women. Women in the lowest birth weight tertile (2.5–6.8 lb, mean weight = 5.5 lb) had nearly 2.5 times the risk of developing the metabolic syndrome. Women with a low birth weight who became adults in the highest tertile of BMI (>25.2 kg/m^2) or waist circumference (>80.7 cm) had nearly a 30% prevalence of the metabolic syndrome.

These results support the fetal origins hypothesis, which contends that undernutrition during developmentally sensitive periods causes an adaptation response by the fetus resulting in programmed altered metabolism, hormonal axes, and organ structure (8,9). Low birth weight is presumed to indicate undernutrition of the fetus in utero. This hypothesis has received support from other epidemiological studies linking low birth weight to coronary heart disease (21), type 2 diabetes (11,22), and hypertension (10,23). Animal studies have been cited as evidence for a programming mechanism (24–28) and have been recently reviewed (29,30). In addition to animal evidence, reports of increased rates of glucose intolerance in adults born during the Dutch famine of the 1940s supports the thesis that maternal nutrition during pregnancy is crucial to future development of metabolic disease (31).

Although several studies have considered the association of birth weight to individual components of the metabolic syndrome, to our knowledge, only two other studies examined the relation of birth weight to the syndrome itself (8,14), and neither study focused on older women. Valdez et al. (14) investigated the syndrome in a biethnic population (Mexican-American and non-Hispanic whites) who were young adult participants in the San Antonio Heart Study, and Barker et al. (8) investigated the metabolic syndrome in a middle-aged British population. Despite some differences in the definition of the metabolic

Table 5—*Age-adjusted comparison of altered glucose tolerance, hypertension, dyslipidemia, and the metabolic syndrome by birth weight tertile*

	Birth weight tertile				
	Low (n = 92)	Middle (n = 112)	High (n = 99)	P value for trend	Odds ratio (95% CI)
Altered glucose tolerance	39.4	39.5	37.6	NS	1.09 (0.78–1.52)
Hypertension	44.0	43.5	38.0	NS	1.13 (0.81–1.58)
Dyslipidemia	40.0	29.8	18.6	<0.01	1.76 (1.19–2.61)
Metabolic syndrome	12.0	9.1	4.3	<0.05	2.41 (1.06–5.51)

Data are %. Odds ratio compares lowest to highest birth weight tertile. Altered glucose tolerance equals fasting plasma glucose ≥6.1 mmol/l and/or postchallenge plasma glucose ≥7.8 mmol/l and/or use of antidiabetic medications. Hypertension equals systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medications. Dyslipidemia equals triglycerides ≥2.3 mmol/l and/or HDL cholesterol ≤1.4 mmol/l. Metabolic syndrome equals combined presence of altered glucose tolerance, hypertension, and dyslipidemia. NS, $P > 0.10$.

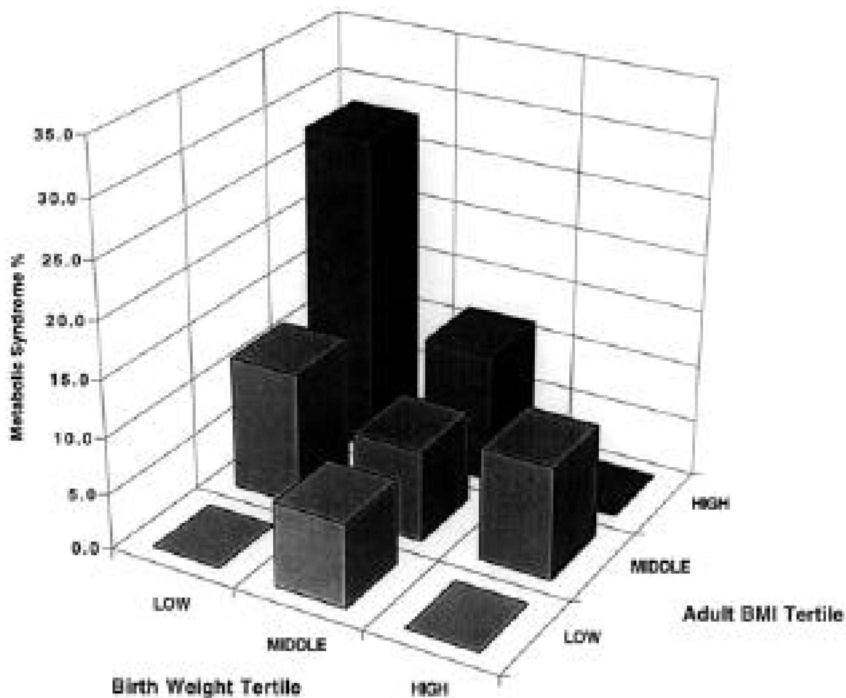

Figure 1—*Combined effects of birth weight (in tertiles) and adult BMI (in tertiles) on the prevalence of the metabolic syndrome in 303 women.*

syndrome, its prevalence was 7.9% among the non-Hispanic white women in Texas, and 6.4% among the British men and women (combined), remarkably similar to the 7.9% prevalence in this study. In accord with the present study, each of the previous studies reported that small babies who became overweight adults had the highest risk of developing the metabolic syndrome.

Adult obesity (especially intra-abdominal obesity) has been implicated as a major risk factor in the metabolic syndrome and cardiovascular disease (3,32–34). Prospective studies (35–37), which tracked obesity from childhood into adulthood, have reported that overweight children have an increased risk of becoming obese adults. In accord with other studies (15,38), the results of the present study also suggest that birth weight tracks into adulthood, with those in the highest birth weight category having the highest adult BMI, waist circumference, current weight, and maximum lifetime weight, but not waist-to-hip ratio (14). Waist circumference has been shown to be a better marker for intra-abdominal fat than waist-to-hip ratio in older adults (39,40). Despite the association of birth weight with adult weight, even into old age, women in the present study who were in the lowest birth weight tertile and the highest weight or waist circumference tertile had the highest prevalence of the metabolic syndrome (30%); thus suggesting that the combination of low birth weight with adult obesity is remarkably dangerous.

One limitation of the present study is the availability and validity of self-reported birth weight. Only 24% of the eligible women had usable birth weight data, and only half of these had paper documentation. Many of these women were born before states began retaining records and issuing birth certificates; furthermore, a high proportion of babies were born out of hospital without a reliable birth weight measurement. Nevertheless, two studies of women have demonstrated that self-reported birth weights are highly correlated to actual birth weights validated using official registries (41,42), and both concluded that self-reported birth weights are reliable for use in epidemiological studies. There were few significant differences between those who did and did not report birth weight. With the exception of age, these differences were small and would have introduced a conservative bias.

Survivor bias is a universal problem in studies of older adults. Low birth weight babies who survived during the years women in this cohort were born were probably healthier than those who did not survive. Selective survival of healthier low birth weight individuals may underrepresent the association of birth weight and the metabolic syndrome in adult life. Nevertheless, a significant trend of metabolic syndrome

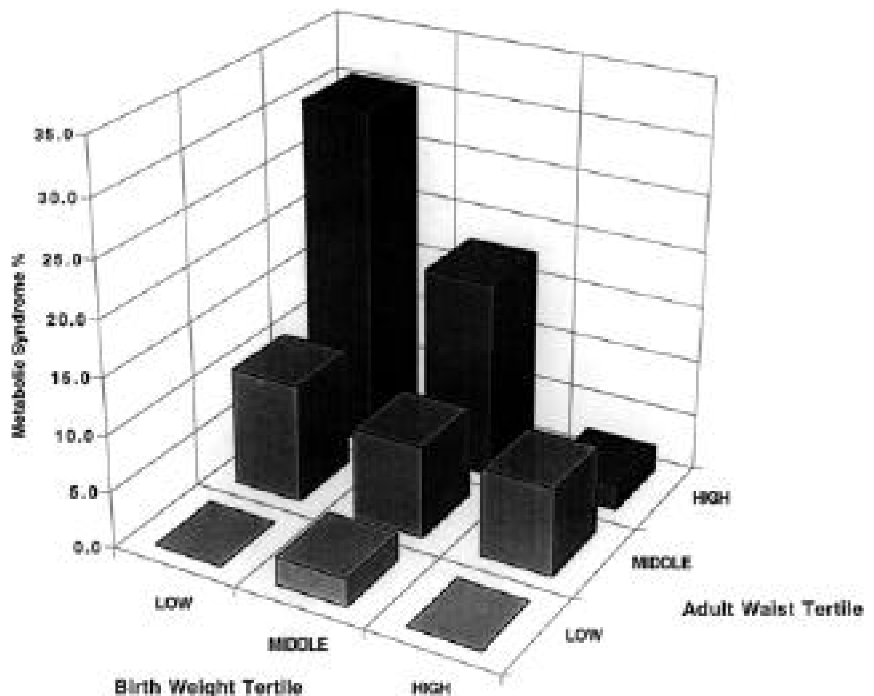

Figure 2—*Combined effects of birth weight (in tertiles) and adult waist circumference (in tertiles) on the prevalence of the metabolic syndrome in 303 women.*

from low to high birth weight categories remains in the seventh decade of life. In addition, with the advancement of neonatal medicine, more babies with much lower birth weights survive today than 50 or more years ago when women in this study were born. The significant increase in the metabolic syndrome in this study despite relatively few very small babies may be magnified in the future. Finally, it is important to note that this association was observed in a relatively lean older cohort; only 27% of women had a BMI >26 kg/m².

The long-term health effects of low birth weight may be confounded by low socioeconomic status (SES) (43). Babies born into low SES tend to be of lower birth weight; if these individuals remain in low SES strata as adults, then increased rates of disease could be related to SES rather than low birth weight. This confounding is unlikely to have affected the present study since essentially all participants were middle to upper-middle class adults based on education and occupation (Hollingshead Index I–III) (44). In addition, several studies have reported associations between fetal influences and future development of metabolic disease independent of SES (45–47).

In summary, this study of postmenopausal women shows that low birth weight is associated with the metabolic syndrome in the seventh decade of life despite the few very small babies and the homogeneous SES of the cohort. The prevalence of the metabolic syndrome was dramatically higher among low birth weight women who became obese adults, indicating that intrauterine environment and prevention of adult overweight are both important in the etiology of the metabolic syndrome. Future research should focus on elucidating the underlying mechanisms with the ultimate goal of developing strategies to ensure proper nutrition in pregnancy and a lifetime of appropriate weight management.

Acknowledgments — This study was supported by the National Institute of Diabetes, Digestive and Kidney Diseases Grant DK-31801. D.E.Y. was supported by the National Institutes of Health Grant T35HL-07473, short-term training for students in health professional schools. He is currently an MD candidate at the University of Alabama School of Medicine.

References

1. Assmann G, Schulte H: The Prospective Cardiovascular Munster (PROCAM) study: prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *Am Heart J* 116:1713–1724, 1988
2. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
3. Kaplan NM: The deadly quartet: upper-body adiposity, glucose intolerance, hypertriglyeridemia and hypertension. *Arch Intern Med* 149:1514–1520, 1989
4. Hjermann I: The metabolic cardiovascular syndrome: syndrome X, Reaven's syndrome, insulin resistance syndrome, atherothrombogenic syndrome. *J Cardiovasc Pharmacol* 20 (Suppl. 8):S5–S10, 1992
5. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 41:715–722, 1992
6. Kaplan NM: Syndromes X: two too many. *Am J Cardiol* 69:1643–1644, 1992
7. Jarrett RJ: In defense of insulin: a critique of syndrome X. *Lancet* 340:469–471, 1992
8. Barker DJP, Hales CN, Fall CHD, Osmond C, Phipps K, Clark PMS: Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 36:62–67, 1993
9. Barker DJP: Fetal origins of coronary heart disease. *BMJ* 311:171–174, 1995
10. Leon DA, Koupilova I, Lithell HO, Berglund L, Mhosen R, Vagero D, Lithell UB, McKeigue PM: Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50-year old Swedish men. *BMJ* 312:401–406, 1996
11. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell UB, Leon DA: Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *BMJ* 312:406–410, 1996
12. Stein CE, Fall CHD, Kumaran K, Osmond C, Cox V, Barker DJP: Fetal growth and coronary heart disease in South India. *Lancet* 348:1269–1273, 1996
13. McCance DR, Pettitt DJ, Hanson RL, Jacobsson LTH, Knowler WC, Bennett PH: Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype. *BMJ* 308:942–945, 1994
14. Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP: Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* 37:624–631, 1994
15. Curhan GC, Willett WC, Rimm EB, Spiegelman D, Ascherio AL, Stampfer MJ: Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. *Circulation* 94:3246–3250, 1996
16. Wingard DL, Sinsheimer P, Barrett-Connor E, McPhillips J: The prevalence of non-insulin dependent diabetes mellitus in older adults: a community-based study. *Diabetes Care* 13 (Suppl. 2):3–8, 1990
17. Hypertension Detection and Follow-Up Program Cooperative Group: The Hypertension Detection and Follow-Up Program. *Prev Med* 5:207–215, 1976
18. Lipid Research Clinics Program Manual of Laboratory Operations. *Vol 1. Lipid and Lipoprotein Analysis.* 2nd ed. Washington, DC, U.S. Govt. Printing Office, U.S. Dept. of Health, Education, and Welfare, 1974 (NIH publ. no. 75–628)
19. Friedewald WJ, Levy RI, Fredrickson DS: Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
20. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
21. Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS: Fetal nutrition and cardiovascular disease in adult life. *Lancet* 341:938–941, 1993
22. Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, Winter PD: Fetal and infant growth and impaired glucose tolerance at age 64 years. *BMJ* 303:1019–1022, 1991
23. Law CM, de Swiet M, Osmond C, Fayers PM, Barker DJP, Cruddas AM, Fall CHD: Initiation of hypertension in utero and its amplification throughout life. *BMJ* 306:24–27, 1993
24. McCance RA, Widdowson EM: The determinants of growth and form. *Proc R Soc Lond* 185:1–17, 1974
25. Winick M, Noble A: Cellular response in rats during malnutrition at various ages. *J Nutr* 89:300–306, 1966
26. Langley SC, Jackson AA: Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. *Clin Sci* 86:217–222, 1994
27. Garofano A, Czernichow P, Breant B: In utero undernutrition impairs rat beta-cell development. *Diabetologia* 40:1231–1234, 1997
28. Iglesias-Barreira V, Ahn MT, Reusens B, Dahri S, Hoet JJ, Remacle C: Pre- and postnatal low protein diet affect pancreatic islet blood flow and insulin release in adult rats. *Endocrinology* 137:3797–3801, 1996
29. Desai M, Hales CN: Role of fetal and infant growth in programming metabolism in later life. *Biol Rev Camb Philos Soc* 72:329–348, 1997
30. Godfrey KM, Barker DJ: Maternal nutrition in relation to fetal and placental growth. *Eur J Obstet Gynecol Reprod Biol* 61:15–22, 1995
31. Ravelli ACJ, Van der Meulen JHP, Michels RPJ, Osmond C, Barker DJP, Hales CN, Bleker OP: Glucose intolerance in adults

after prenatal exposure to famine. *Lancet* 351:173–177, 1998
32. Despres JP: Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition* 9:452–459, 1993
33. Bjorntorp P: Abdominal fat distribution and the metabolic syndrome. *J Cardiovasc Pharmacol* 20 (Suppl. 8):S26–S28, 1992
34. Wajchenberg BL, Malerbi DA, Rocha MS, Lerario AC, Santomauro AT: Syndrome X: a syndrome of insulin resistance: epidemiological and clinical evidence. *Diabetes Metab Rev* 10:19–29, 1994
35. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH: Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med* 337:869–873, 1997
36. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T: Do obese children become obese adults? A review of the literature. *Prev Med* 22:167–177, 1993
37. Guo SS, Roche AF, Chumlea WC, Gardner JD, Siervogel RM: The predictive value of childhood body mass index values for overweight at age 35 years. *Am J Clin Nutr* 59:810–819, 1994
38. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ: Birth weight and adult hypertension and obesity in women. *Circulation* 94:1310–1315, 1996
39. Goodman-Gruen D, Barrett-Connor E: Sex differences in measures of body fat and body fat distribution in the elderly. *Am J Epidemiol* 143:898–906, 1996
40. Despres JP, Prud'homme D, Pouliot MC, Tremblay A, Bouchard C: Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. *Am J Clin Nutr* 54:471–477, 1991
41. Little RE: Birthweight and gestational age: mother's estimates compared with state and hospital records. *Am J Public Health* 76:1350–1351, 1986
42. Troy LM, Michels KB, Hunter DJ, Spiegelman D, Manson JE, Colditz GA, Stampfer MJ, Willett WC: Self-reported birth weight and history of having been breast-fed among younger women: an assessment of validity. *Int J Epidemiol* 25:122–127, 1996
43. Elford J, Whincup P, Shaper AG: Early life experience and adult cardiovascular disease: longitudinal and case-control studies. *Int J Epidemiol* 20:833–844, 1991
44. Kritz-Silverstein D, Wingard DL, Barrett-Connor E: Employment status and heart disease risk factors in middle-aged women: the Rancho Bernardo Study. *Am J Public Health* 82:215–219, 1992
45. Gaillard TR, Schuster DP, Bossetti BM, Green PA, Osei K: The impact of socioeconomic status on cardiovascular risk factors in African-Americans at high risk for type II diabetes: implications for syndrome X. *Diabetes Care* 20:745–752, 1997
46. Koupilova I, Leon DA, Vagero D: Can confounding by sociodemographic and behavioural factors explain the association between size at birth and blood pressure at age 50 in Sweden? *J Epidemiol Community Health* 51:14–18, 1997
47. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD: Birthweight, body mass index in middle age, and incident coronary heart disease. *Lancet* 348:1478–1480, 1996