Nongenetic Influences of Obesity on Other Cardiovascular Disease Risk Factors: An Analysis of Identical Twins

BETH NEWMAN, PHD, JOSEPH V. SELBY, MD, CHARLES P. QUESENBERRY, JR., PHD, MARY-CLAIRE KING, PHD, GARY D. FRIEDMAN, MD, AND RICHARD R. FABSITZ, MA

Abstract: The importance of genetic influences on obesity has been emphasized recently. We conducted matched co-twin analyses of 250 pairs of White, male, monozygotic twins from the National Heart, Lung, and Blood Institute (NHLBI) Twin Study. Entirely in the absence of genetic influences, obesity was significantly associated with systolic and diastolic blood pressures; one-hour, post-load glucose; total, LDL-, and HDL-cholesterol; and triglycerides among these 42–55 year old men. Similar results were obtained in longitudinal analyses of weight change during adulthood (from mean age of 20 to mean age of 48 years) and risk factor status at middle-age. These results indicate that behaviors and environmental exposures that occur later in life are responsible, at least in part, for the associations between adult obesity and cardiovascular disease risk, supporting the appropriateness of weight reduction efforts during adulthood. (*Am J Public Health* 1990; 80:675–678.)

Introduction

Obesity, hypertension, glucose intolerance, and high lipid levels tend to cluster in families.[1,2] Obesity is also correlated with these other cardiovascular disease risk factors in individuals.[3,4] The extent to which this clustering is caused by common genetic influences on multiple risk factors or by shared environmental or behavioral factors is unknown. In a previous report,[5] investigators from the National Heart, Lung, and Blood Institute (NHLBI) Twin Study demonstrated that many cardiovascular disease risk factors have genetic determinants. Using another analytic approach with the same data, we sought to determine whether associations exist between obesity and the other cardiovascular disease risk factors independent of genetic influences.

Comparison within genetically identical, monozygotic twin pairs removes all genetic variability.[6] If intrapair differences in cardiovascular disease risk factors are related to intrapair differences in obesity, these associations must be attributable to environmental or behavioral, and therefore potentially alterable, influences. In this paper, we use longitudinal data from a group of White, male, monozygotic twins in a matched-pair analysis to assess the nature of the relationships of obesity and adult weight gain with blood pressure, glucose tolerance, and lipid levels at middle-age.

Methods

Study Subjects

Data collection for the NHLBI Twin Study took place between July 1969 and June 1973 in five locations: Framingham, Massachusetts; Indianapolis, Indiana; and Los Angeles, San Francisco, and Davis, California. Participants were 514 pairs of White male twins who were members of the National Academy of Sciences-National Research Council Twin Panel[7] and who lived in California, New England, or within 200 miles of Indianapolis. All twins were born during the years 1917 through 1927 and served in the US Armed Forces during the period from World War II through the Korean War. Twins were ages 42–55 years at the study examination. In this report, only the 250 monozygotic twin pairs were included.

Data Collection

After an overnight fast, both members of each twin pair received physical examinations on the same day by different physicians. Weight and height were measured in pounds and inches. Each individual's weight and height also were obtained from records of the physical examination prior to military induction (ages 17 to 28). After conversion to kilograms and meters, body mass index (BMI) was calculated as the measure of obesity (weight/height^2). Blood pressure was measured three times using a standard sphygmomanometer: first by a nurse, later twice by a physician. The participant was seated, and both systolic and diastolic (Phase V) blood pressures were recorded. The mean of the two physician readings was used in this report. Blood samples were collected to determine glucose tolerance, plasma cholesterol and triglycerides, and serotypes for assignment of zygosity. A 50-g oral glucose load was given one hour before blood was drawn unless the subject had diabetes and was currently using insulin or oral hypoglycemic agents or had glycosuria of 3+ or greater. Glucose levels were measured at the examination centers using an SMA 12/60 instrument (Technicon Instruments, Tarreytown, NY). Total, HDL-, and LDL-cholesterol[8] and triglyceride[9] levels were determined at three regional laboratories; specimens were exchanged to maintain standardization. Additional details of the recruitment process, response rates, zygosity determination, clinical examination, and questionnaire are available.[5,10]

Statistical Analyses

Matched-pair t-tests and linear regression models were computed using SAS computer programs.[11] Both members of a twin pair were included in both the unmatched and matched analyses. However, unmatched analyses were adjusted to avoid overestimating the statistical significance of parameter estimates due to correlated errors between co-twins.[12] For the matched analyses, regression models incorporated intrapair differences of the dependent and independent variables.

From the Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA (Newman, Selby, Quesenberry, Friedman); University of California-Berkeley, School of Public Health (Newman, King); and the Clinical and Genetic Epidemiology Branch, National Heart, Lung, and Blood Institute, Bethesda, MD (Fabsitz). Address reprint requests to Beth Newman, PhD, Division of Research, Kaiser Permanente Medical Care Program, Northern California Region, 3451 Piedmont Avenue, Oakland, CA 94611. This paper, submitted to the Journal August 28, 1989, was revised and accepted for publication December 7, 1989.

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The intrapair difference for each variable was obtained by subtracting the value for one twin from that of the other in each monozygotic twin pair. For analyses of weight change, the value of BMI at the military induction physical examination was subtracted from the value of BMI at the study examination.

Sample sizes varied between 219 and 245 pairs in the different regression analyses because of missing values and specific exclusions of individuals using medications that affect blood pressure, glucose, or lipid levels. Because the distribution of triglycerides was skewed toward higher values, we used the natural log transformation on this variable in all regression analyses.

Results

Means and standard deviations for obesity, weight change, and the other cardiovascular disease risk factors for the twins as individuals are presented in Table 1.

Within monozygotic twin pairs, heavier twins had significantly higher levels of systolic and diastolic blood pressures, glucose (one-hour, post-load), total cholesterol, LDL-cholesterol, and triglycerides and lower levels of HDL-cholesterol than their genetically identical, lighter-weight brothers (Table 2). Regression coefficients measuring the association of obesity with each risk factor are indicated in Table 3. Examination BMI was significantly associated with all the cardiovascular disease risk factors in the unmatched analyses, independently of age. Matched-pair regression analyses revealed even stronger, significant, cross-sectional relationships between BMI and the cardiovascular disease risk factors. Only the regression coefficient for HDL-cholesterol was somewhat reduced.

Obesity was then partitioned into two variables—BMI at military induction (average age 20 years), and change in BMI during the 20 to 34 years between the induction and study examinations. The independent influences of the two obesity parameters on the other cardiovascular disease risk factors are indicated in Table 4. In both the unmatched and matched analyses, weight gain during adulthood was significantly associated with all the cardiovascular disease risk factors measured. In addition, induction BMI was independently and significantly related to systolic and diastolic blood pressures, total cholesterol, and triglycerides in the matched analyses. The negative regression coefficient between change in BMI and HDL-cholesterol was the only coefficient smaller in the matched analysis than in the unmatched analysis; the inverse relationship between induction BMI and HDL-cholesterol in the unmatched analysis was reduced and no longer statistically significant in the matched analysis. The proportion of nongenetic variance explained by both measures of obesity in the matched analyses ranged from 4 percent for HDL-cholesterol to 10 percent for total cholesterol, 11 percent for systolic blood pressure, and 13 percent for diastolic blood pressure and triglycerides.

TABLE 1—Obesity Measures at Military Induction and at Study Examination and Cardiovascular Disease Risk Factors at Study Examination (1969–73) in a Sample of White, Male, Monozygotic Twins

Variables	Number of Individuals	Mean ± Standard Deviation
Body mass index (kg/m^2)		
at military induction	499	21.9 ± 2.4
at study examination	499	25.7 ± 3.2
change between induction and examination	498	3.8 ± 2.9
Age at study examination (years)	500	47.8 ± 3.1
Systolic blood pressure (mmHg)	439	127.0 ± 16.3
Diastolic blood pressure (mmHg)	439	81.3 ± 10.2
One-hour, post-load glucose (mg/dl)	465	162.6 ± 51.9
Total cholesterol (mg/dl)	491	219.7 ± 35.0
HDL-cholesterol (mg/dl)	486	44.2 ± 12.8
LDL-cholesterol (mg/dl)	485	143.5 ± 33.5
Triglycerides (mg/dl)	490	136.1 ± 89.2

TABLE 2—Mean Levels of Cardiovascular Disease Risk Factors at Ages 42–55 Years Comparing Heavier and Lighter Brothers within Monozygotic Twin Pairs

Variables	Heavier Twin	Lighter Twin	Mean Intrapair Difference (95% CI)
Body mass index (kg/m^2)	26.6	24.8	1.8 (1.6, 2.0)
Systolic blood pressure (mmHg)	129.6	124.5	5.1 (3.1, 7.1)
Diastolic blood pressure (mmHg)	82.7	80.0	2.7 (1.4, 3.9)
One-hour, post-load glucose (mg/dl)*	161.7	156.0	5.6 (0.3, 11.2)
Total cholesterol (mg/dl)*	222.6	217.1	5.5 (1.9, 9.1)
HDL-cholesterol (mg/dl)*	43.1	45.3	−2.2 (−3.5, −1.0)
LDL-cholesterol (mg/dl)*	145.7	141.6	4.2 (0.8, 7.5)
Triglycerides (mg/dl)*	147.6	124.9	22.7 (12.5, 33.0)

*Conversion factor to SI Units in mmol/L:
Glucose—0.05551
Cholesterol (total, HDL, LDL)—0.02586
Triglycerides—0.01129

TABLE 3—Regression Coefficients† (± standard errors) for Cross-sectional Relationships between Body Mass Index (BMI) and other Cardiovascular Disease Risk Factors in Middle-Aged, White, Male Monozygotic Twins

Dependent Variables	Unmatched Analysis	Matched Analysis
Systolic blood pressure	1.47 ± 0.28	2.23 ± 0.43
Diastolic blood pressure	1.06 ± 0.17	1.44 ± 0.26
One-hour, post-load glucose	3.95 ± 0.80	4.79 ± 1.22
Total cholesterol	2.43 ± 0.51	3.88 ± 0.74
HDL-cholesterol	−0.97 ± 0.18	−0.83 ± 0.27
LDL-cholesterol	1.13 ± 0.49	2.37 ± 0.71
Ln triglycerides	0.065 ± 0.008	0.073 ± 0.013

†Coefficients are age-adjusted: age was included in the unmatched regression models, but was not related significantly to any outcome; matched co-twin analyses control for age in that co-twins are perfectly matched on age.

Discussion

In response to the recent emphasis on the importance of genes in influencing adult obesity,[13–15] we used data from identical twins to address the following question: do nongenetic differences in obesity contribute to levels of blood pressure, glucose intolerance, and lipids? The results of our analyses indicate that significant associations exist between obesity and many cardiovascular disease risk factors entirely in the absence of genetic influences. These results were obtained from both cross-sectional analyses of obesity and concurrent risk factor status and longitudinal analyses of change in weight during adulthood and risk factor status during middle-age. Furthermore, because matched-pair analyses also control for any factors that are identical or very similar between co-twins, such as the influences of shared early environment and culture, the observed associations

TABLE 4—Regression Coefficients[+] (±standard errors) for Longitudinal Relationships between Cardiovascular Disease Risk Factors and Body Mass Index (BMI) from Military Induction to Middle-age in White, Male, Monozygotic Twins

Dependent Variables	Unmatched Analysis		Matched Analysis	
	Change in BMI	Induction BMI	Change in BMI	Induction BMI
Systolic blood pressure	1.66 ± 0.31	1.06 ± 0.39	2.27 ± 0.44	1.93 ± 0.79
Diastolic blood pressure	1.18 ± 0.19	0.79 ± 0.24	1.48 ± 0.26	1.09 ± 0.47
One-hour, post-load glucose	4.60 ± 0.87	2.19 ± 1.21	4.99 ± 1.25	3.22 ± 2.29
Total cholesterol	2.83 ± 0.55	1.33 ± 0.77	3.89 ± 0.76	3.80 ± 1.37
HDL-cholesterol	−0.97 ± 0.20	−0.97 ± 0.28	−0.84 ± 0.27	−0.75 ± 0.50
LDL-cholesterol	1.34 ± 0.54	0.54 ± 0.76	2.35 ± 0.72	2.55 ± 1.33
Ln triglycerides	0.075 ± 0.008	0.041 ± 0.011	0.075 ± 0.013	0.057 ± 0.023

[+]Coefficients are age-adjusted: age was included in the unmatched regression models, but was not related significantly to any outcome; matched co-twin analyses control for age in that co-twins are perfectly matched on age.

may be attributed more specifically to environmental exposures or personal behaviors of adulthood.

These results do not preclude genetic influences on obesity, blood pressure, glucose tolerance, or lipid levels.[5,16] Nor do they reveal the specific, nongenetic mechanisms underlying the associations of cardiovascular disease risk factors with obesity. Obesity may serve as a marker of an atherogenic lifestyle, or it may contribute directly to the increases in blood pressure, glucose intolerance, and lipid levels through mechanical or biochemical pathways. Regardless of the mechanisms involved, the effects observed here are not pleiotropic effects of genes regulating adult fatness. The generalizability of these findings is supported by the comparability of the twins participating in this study to White men in the general population[17–19] and to participants in similar studies.[20–23]

Weight change during adulthood was generally more important than baseline BMI at military induction in predicting cardiovascular disease risk factor status in the longitudinal analyses. However, for blood pressure, total cholesterol, and triglycerides, BMI in early adulthood also contributed independently to risk factor status in middle-age. When analyses for all cardiovascular disease risk factors were conducted including both examination BMI (middle-age) and induction BMI (early adulthood) in the models, only the examination BMI was statistically significant (data not shown). These results suggest that the attained level of obesity is important in elevating a person's risk for diabetes and cardiovascular disease, although duration of obesity may also play an independent role.

Although the influence of obesity on the other cardiovascular disease risk factors appears to be limited to less than 15 percent of the nongenetic variability of each risk factor, a significant, if moderate, effect of weight gain during adulthood was observed on each risk factor. The average man in our cohort was 69 inches tall and gained 28 pounds between age 20 and age 48. By middle-age, he had higher levels of each of the cardiovascular disease risk factors studied, except for HDL-cholesterol, than men who gained less weight. Associated with his weight gain were excesses of 9.5 mmHg systolic blood pressure, 6.2 mmHg diastolic blood pressure, 21.0 mg/dl glucose (one-hour, post-load), 16.4 mg/dl total cholesterol, 9.8 mg/dl LDL-cholesterol, and a decrease of 3.5 mg/dl HDL-cholesterol. Similarly, his triglyceride level was 40 percent higher than that of men who did not gain weight between military induction and middle-age; this represents roughly a 50 mg/dl excess. These excesses occurred independent of initial BMI and can be attributed solely to nongenetic influences on the basis of the matched co-twin analysis (Table 4). The cumulative impact of similar or larger weight gains on multiple risk factors clearly contributes significantly to an increase in cardiovascular disease risk.

The causes of adult obesity are complex and undoubtedly involve both genetic and nongenetic influences.[24,25] Bouchard, *et al*,[26] have shown that monozygotic twins generally gain similar amounts of weight as a result of similar diets that include excess calories. However, unrelated twin pairs respond very differently to the same diet. This interpair variability is a reflection of gene-environment interaction, where an individual's response depends both on genetic predisposition as well as specific environmental exposure. Moreover, BMI is only a surrogate measure of obesity and may not capture the most relevant aspect related to cardiovascular disease risk. Unfortunately, more detailed measures of total body fat or fat distribution were not available from the induction or 1969–73 study examinations.

Despite the etiologic complexity of adult obesity, and the well-documented difficulty in its control, our findings provide some reason for optimism. They indicate that behaviors and environmental exposures that occur later in life are responsible, in part, for the association between adult obesity and cardiovascular disease risk factor status. They emphasize the importance of attained weight in influencing that risk, thereby suggesting that weight reduction will be effective even at later ages, when most individuals tend to gain weight. Thus, they confirm the clinical impression that weight control and prevention of obesity are likely to be successful in reducing a person's risk of cardiovascular disease and diabetes.

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