A Twin Study of Human Obesity

Albert J. Stunkard, MD; Terryl T. Foch, PhD; Zdenek Hrubec, ScD

Height, weight, and body mass index (BMI) were assessed in a sample of 1974 monozygotic and 2097 dizygotic male twin pairs. Concordance rates for different degrees of overweight were twice as high for monozygotic twins as for dizygotic twins. Classic twin methods estimated a high heritability for height, weight, and BMI, both at age 20 years (.80, .78, and .77, respectively) and at a 25-year follow-up (.80, .81, and .84, respectively). Height, weight, and BMI were highly correlated across time, and a path analysis suggested that the major part of that covariation was genetic. These results are similar to those of other twin studies of these measures and suggest that human fatness is under substantial genetic control.

(*JAMA* 1986;256:51-54)

HEREDITY clearly can play a role in obesity. Millenia of experience with farm animals and the existence of several forms of genetic obesity in rodents[1] attest to the genetic potential for obesity. We do not, however, know the extent to which this genetic potential is expressed in humans. Human obesity "runs in families,"[2-4] but family studies cannot separate the influences of heredity and environment. Five large twin studies have investigated height and weight independently of each other and found that height is quite heritable and weight less so.[5-9] Because they did not assess weight in relation to height, they convey no information about the heritability of overweight or obesity. Two twin studies of children[10,11] and two of adults,[12-14] however, have performed such assessment and have found evidence of genetic determination of human obesity. This report describes the results of the largest twin study of human obesity yet undertaken, to the best of our knowledge.

POPULATION AND METHODS

The sample was drawn from the Twin Registry maintained by the National Academy of Sciences–National Research Council (NAS-NRC) since 1955. The construction of the NAS-NRC Twin Registry panel and the methods of compiling medical information and classifying zygosity have been described elsewhere.[15,16] The registry contains information about 15 924 male twin pairs who were born between 1917 and 1927 and who served in the armed forces during World War II or in Korea. Zygosity was determined by blood typing for 806 pairs, by fingerprinting for 1947 pairs, and by questionnaire for 10 732 pairs. Zygosity could not be determined for 2439 pairs, which were excluded from further analysis.

Weight and height, measured during the induction physical examination at age 20±2.6 years (range, 15 to 28 years), were available for 5884 monozygotic (MZ) pairs and 7492 dizygotic (DZ) pairs. In 1967, a questionnaire was mailed to 3248 MZ and 3824 DZ pairs, then 40 to 50 years of age, asking for reports of height and weight at that time and at age 25 years. Replies to this 25-year follow-up were received from 1974 MZ pairs and 2097 DZ pairs for whom induction data were also available. This sample was utilized for the analyses.

Two measures of fatness were used: the body mass index (BMI), ie, weight in kilograms divided by height in meters squared,[17] and percentage overweight according to the Fogarty tables of recommended weight.[18]

The mean values for height, weight, and BMI of those twins who participated in the follow-up did not differ from the means of the entire sample at induction, indicating no selection bias in the study sample. Height, weight, and BMI were not correlated with age in the MZ and DZ samples at induction and at follow-up, perhaps because of the narrow range, so that corrections for age were not required. Table 1 shows that the height, weight, and BMI of DZ twins were slightly larger than those of MZ twins at induction and at the 25-year follow-up. These differences, on the order of one tenth of 1 SD, are statistically significant only because of the very large sample size. No differences in the variances of these values between MZ and DZ twins in the study sample were found by the Bartlett-Box F test for homogeneity of variance.[19] Thus, the data meet a key requirement of classic twin analysis.

The Figure shows the distribution of the BMI of both MZ and DZ twins at induction when they averaged 20 years of age and at the follow-up when they averaged 45 years. The slightly larger BMI of the DZ twins was present throughout the distribution. During the 25 years between the two assessments, while the mean BMI was increasing significantly, the distributions remained symmetric.

The first method of study consisted of determining concordance rates for MZ and DZ twins. Since there was no natural cutoff point for obesity in the distribution of BMI, arbitrary cutoff points were selected: 15%, 20%, 25%, 30%, 35%, and 40% overweight.[18] The significance of the difference between the concordance rates of MZ and DZ twins was assessed by the χ^2 test.

The second method of study was Falconer's widely utilized method of estimating heritability.[20,21] This method determines how much less similar DZ twins are in respect to the trait under study than are MZ twins (who are genetically identical). The measure of similarity is the correlation coefficient (r) of the trait in DZ twins, which is subtracted from the correlation coefficient of MZ twins. The resultant estimate of heritability, sometimes denoted G, is $2(r_{MZ}-r_{DZ})$.

The third method of study used a path model[22] to estimate genetic and environmental contributions to stability in height, weight, and BMI during the 25 years between induction and follow-up. Correlation coefficients were calculated between phenotypic values at induction and at the follow-up 25 years later. The heritability estimates noted below were used to estimate the separate genetic and environmental contributions to long-term stability.

From the Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia (Dr Stunkard); and the Medical Follow-up Agency, National Academy of Sciences–National Research Council, Washington, DC (Dr Hrubec). Dr Foch was formerly with the Pennsylvania State University. Dr Hrubec is now with the Radiation Epidemiology Branch, National Cancer Institute, Bethesda, Md.

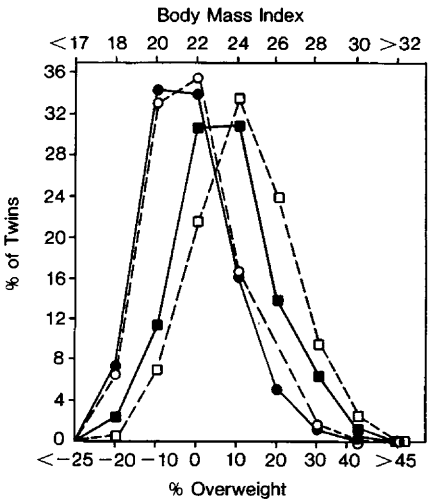
Reprint requests to 133 S 36th St, Philadelphia, PA 19104 (Dr Stunkard).

Downloaded From: by a Rijksuniversiteit Groningen User on 11/28/2017

Table 1.—Characteristics of the Study Sample*

	Monozygotic Twins		Dizygotic Twins			
	Mean	SD	Mean	SD	F	Bartlett-Box F
Induction						
Height, cm	172.52 (171.83)	6.48 (6.44)	173.43 (172.45)	6.43 (6.50)	40.88† (61.54†)	0.227 (1.404)
Weight, kg	65.26 (64.89)	8.40 (8.34)	66.22 (65.93)	8.40 (8.59)	26.49† (98.25†)	0.011 (11.361‡)
Body mass index	21.91 (21.89)	2.47 (2.46)	21.99 (22.06)	2.41 (2.51)	2.35 (31.29†)	2.138 (4.95§)
25-y follow-up						
Height, cm	176.64	6.48	177.60	6.48	44.55†	0.009
Weight, kg	77.67	9.83	78.33	10.10	8.90‡	3.190
Body mass index	24.86	2.70	24.80	2.71	1.275	0.081

*The numbers in parentheses represent the values of all members of the Twin Registry of the National Academy of Sciences-National Research Council. Heights and weights were obtained for both twins at induction and also at the 25-year follow-up for 1974 monozygotic pairs and 2097 dizygotic pairs.
†$P<.001$. ‡$P<.01$. §$P<.05$.



Distribution of percentage overweight and body mass index (BMI) of monozygotic (solid lines) and dizygotic twins (broken lines) at induction (circles) when they averaged 20 years of age and at 25-year follow-up (squares). Percentage overweight, calculated from Fogarty tables of recommended weight[18] on lower horizontal axis, corresponding body mass index on upper horizontal axis. Note marked upward shift of distribution at 25-year follow-up, while its form remains symmetrical.

Table 2.—Probandwise Concordance Rates for Various Percentages of Overweight*

	At Induction			At Follow-up		
	% Concordant			§ Concordant		
% Overweight	Monozygotic Twins	Dizygotic Twins	χ^2 (1 *df*)	Monozygotic Twins	Dizygotic Twins	χ^2 (1 *df*)
15	61 (8.7)	31 (8.7)	66.05	68 (39.6)	49 (39.1)	113.41
20	57 (4.9)	27 (5.1)	37.78	60 (26.2)	40 (26.9)	80.74
25	46 (2.5)	24 (2.8)	11.68	54 (15.0)	26 (15.2)	103.83
30	51 (1.4)	19 (1.5)	13.30	47 (8.3)	16 (8.3)	76.15
35	44 (0.8)	12 (0.8)	8.18	43 (4.7)	9 (4.3)	55.58
40	44 (0.5)	0 (0.3)	7.66	36 (2.4)	6 (2.2)	24.53

*Each twin whose weight exceeded a given criterion was included as a proband. Percentages in parentheses represent the prevalence of overweight twins at a given criterion level. For 1 *df*, the statistical significance of a χ^2 of 7.88 is <.005.

RESULTS

The concordance rates of MZ and DZ twins for six levels of overweight are shown in Table 2. At induction, when the twins averaged 20 years of age, there were few overweight pairs, reflecting the fact that marked obesity was grounds for exclusion from military service. At this time, the concordance rate of MZ twins was far higher than that of DZ twins at all six levels of overweight. Twenty-five years later, when the prevalence of overweight had risen by a factor of five, the concordance rates of MZ twins were still far higher than that of DZ twins. These differences were statistically highly significant.

Estimation of heritability began with calculation of the intraclass correlations between pairs of MZ and DZ twins for height, weight, and BMI. There were large differences between the correlations of MZ and DZ twins, suggesting that genetic factors play an important role. Heritability for BMI was estimated at .77 at induction and .84 at the 25-year follow-up. It appears that about 80% of the variance in BMI is accounted for by genetic factors and that the magnitude of this contribution remains stable throughout adult life. Similar results are shown for height and weight in Table 3.

A method of estimating the influence of environment is based on the assumption that any differences between MZ twin pairs must be environmentally determined. Environmental influences within the family can thus be estimated as the difference between 1.00 and the correlation coefficient for MZ twins. The large intrapair correlations between MZ twins suggest that environmental influences during early adulthood are small—9%, 15%, and 19% for height, weight, and BMI, respectively. At the 25-year follow-up, these influences increased to 12%, 26%, and 33% for height, weight, and BMI, respectively. The magnitude of genetic influences, however, remained stable during this period, since the increase in within-family environmental influences was compensated by a decrease in between-family environmental influence.

The path analysis showed considerable stability over the 25 years from induction to follow-up in the values for height, weight, and BMI. Correlations between these phenotypic values at the two times were .89 for height, .65 for weight, and .54 for BMI. Most of this relative stability is attributable to genetic factors, with genetic correlations between the two time periods even higher than the phenotypic ones—.97 for height, .74 for weight, and .69 for BMI.

Downloaded From: by a Rijksuniversiteit Groningen User on 11/28/2017

Table 3.—Intrapair Correlations (r) for Monozygotic (MZ) and Dizygotic (DZ) Twin Pairs and Heritability (G) With its SE*

	r_{MZ} (1974 Pairs)	r_{DZ} (2097 Pairs)	G	SE*
Induction				
Height	.9055	.5077	.7956	.0344
Weight	.8494	.4591	.7806	.0367
Body mass index	.8096	.4238	.7716	.0390
25-y follow-up				
Height	.8826	.4823	.8006	.0350
Weight	.7447	.3379	.8136	.0436
Body mass index	.6655	.2444	.8422	.0481

*$SE = 2\left[\frac{(1-r_{MZ}^2)^2}{N_{MZ}} + \frac{1-r_{DZ}^2)^2}{N_{DZ}}\right]^{1/2}$

The above formula for SE is derived from Falconer[20] and Loehlin and Nichols.[21]

Table 4.—Heritability Estimates of Twin Studies of Obesity and Other Medical Conditions

Condition	Heritability (G ± SE)
Obesity in children[10]	.77 ± 17 (skinfold thickness)
Obesity in children[11]	.88 (skinfold thickness)
Obesity in adults[12]	Concordance for obesity two times higher among monozygotic than among dizygotic twins
Obesity in adults[13]	.64 (relative weight at age 45 yr)
Obesity in adults[14]	.80 (body mass index at age 20 yr)
Schizophrenia[23]	.68 ± .04
Hypertension[24]	.57 ± .25
Alcoholism[25]	.57
Cirrhosis of the liver[25]	.53
Epilepsy[26]	.50 ± .33
Coronary artery disease[27]	.49 ± .30
Breast cancer[28]	.45 ± .30

COMMENT

The results of three methods of analyzing the data of a large twin register all suggest that human fatness is under strong genetic control. These results agree with those of the only other twin studies of human fatness and obesity.[10-14]

Table 4 shows that in two studies of children, heritability estimates suggest that genetic factors account for 77% and 88%, respectively, of the variance in skinfold thickness and that the proportion of genetic variance apparently increased with increasing age.[10,11] Few obese twins, however, were present in either sample. The study by Medlund et al[12] did include a large number of overweight twins. Using only one cutoff point—20% overweight—these investigators found that the concordance rate for MZ twins was approximately twice as high as that for DZ twins, a result quite similar to that of the present study.

Major contributions to the understanding of genetic factors in obesity have been made by the National Heart, Lung, and Blood Institute's study of 514 twin pairs drawn from the same NAS-NRC Registry used in the present study. Height and weight were measured two to six years after the 25-year follow-up questionnaire. The analysis by Feinleib et al[13] of "relative weight" based on these measurements yielded an estimate of heritability of .64, a value lower than the .84 for BMI in the present study. Later analyses by Fabsitz et al,[14] however, estimated a heritability of .80 for BMI at induction, almost identical to the .77 of the present study.

A perspective on the proportion of genetic variance estimated for obesity is provided by a comparison with the variance estimated for other medical disorders by twin studies. Table 4 shows a genetic determination of fatness or obesity at least as great as that of any of these disorders.

These conclusions are supported also by the results of family studies. Longini and colleagues'[29] analysis of data from the Tecumseh Project estimates that common family environment shared by ordinary siblings living together accounted for only 11% of the variance in BMI, a value even lower than the 19% found at induction in the present study of twins. Similarly, Savard et al[30] found substantial correlations in fatness among first-degree biological relatives and none between spouses even after controlling for several potentially confounding variables.

Two limitations of the study should be noted, one deriving from the nature of the sample and one from interpretation of the results of twin studies. The sample is limited to men who, on induction into the armed forces, had passed a physical examination that screened out obese persons. The study thus provides no information about obesity among women or among men with juvenile-onset obesity.

Twins studies constitute the classic approach to problems of human heredity, and they have a long and venerable history. Comparison of the concordance rates of MZ and DZ twins is a straightforward process that has taught us much of what we know about genetic determinants of human traits. Estimates of heritability, however, are subject to criticism, and many believe that they overestimate the contribution of heredity. Much of the criticism revolves around factors that influence the intrapair correlations between MZ and DZ twins. Since the role of heredity is estimated by the difference in the intrapair correlations between MZ and DZ twins, any nongenetic factors that influence these correlations can bias the results. Most attention has been paid to factors that spuriously inflate correlations between MZ twin pairs. Inflated correlations of MZ twin pairs increase the difference between the intrapair correlations of MZ and DZ twin pairs and make heredity appear more important than it is. It should be noted, however, that the contribution of heredity may also be underestimated by other types of error that result in "reverse bias."

Among the various circumstances that may spuriously *increase* the estimate of heritability is a significant difference in the variances of MZ and DZ twins. In the present study, there was no such difference. Another potential source of bias is the presence of

Downloaded From: by a Rijksuniversiteit Groningen User on 11/28/2017

covariance between genotype and environment, such as greater distribution of obesity-prone persons in environments rich in fatty foods. Fabsitz et al[31] interpreted their finding of difference in dietary habits between MZ and DZ twins as evidence of covariance, but in another study, Fabsitz and colleagues[14] assumed equal covariance for the two types of twins.

Other sources of bias that increase the estimate of heritability include the presence of nonadditive variance, gene-environment interaction, and unequal shared environment of MZ and DZ twins. Twin data alone do not permit testing for these types of bias, and a finding that between-family variances in weight and BMI became slightly negative at the 25-year follow-up suggests that at least one assumption of twin studies was violated.

As noted above, reverse bias may spuriously *decrease* the estimate of heritability, but there was little evidence of such bias in the present study. One form of reverse bias, error in determination of zygosity, is usually in the conservative direction, since MZ pairs mistaken for DZ pairs increase the DZ correlation, while DZ pairs mistaken for MZ pairs decrease the MZ correlation. The result is a decrease in the difference in the intrapair correlations of the two types of twins. This error is unlikely to have played an important part in this study: correct classification was found in 95% of pairs in a subsample of the present population.[13] A second source of reverse bias is assortative mating—the attraction of likes in marital couples. Such mate selection increases the genetic similarity of DZ twins without also increasing the similarity of MZ twins (who are already genetically identical). Again, the result is a decrease in the difference in the intrapair correlations. The third source of conservative error is the "twin transfusion syndrome," which afflicts many of the two thirds of MZ twins who share a common chorion. Those so afflicted are smaller and less robust at birth, which decreases the correlation between them.[32]

At the 25-year follow-up, in addition to the large increase in weight and BMI, Table 1 shows that there was also a 4-cm increase in height. Since this increase occurred in both MZ and DZ twins, it could not have influenced the estimates of heritability. Nevertheless, it deserves explanation. The most reasonable cause appears to have been a combination of two factors—further growth and overestimation of height at follow-up.

Although the mean age of the twins at induction was 20 years, a sizeable proportion were still capable of added growth. Persons born in the early 1920s matured later than those born more recently and, furthermore, 29% of the twins were aged 18 years or younger at induction. Johnston has calculated that a sample with these characteristics would show a 2-cm increase in height before cessation of growth (F. E. Johnson, PhD, oral communication, March 1986).

The opportunity for overestimation of height at follow-up occurred because, although height at induction was measured, height at follow-up was derived from self-report. Palta et al[33] have shown that self-reports by men overestimate height by 2.3 cm. Together these two sources yield an increase in height of at least 4 cm.

Twin studies constitute an important first step in identifying genetic influences in humans, and these studies suggest a strong genetic influence on human fatness and obesity. This suggestion is supported by the results of a very recent adoption study, which has confirmed the importance of genetic influences on human fatness.[34]

This work is one of a program of collaborative studies that make use of the NAS-NRC Twin Registry. The use of records provided by the registry, the Department of Defense, the Veterans Administration, and the National Archives and Records Service of the General Services Administration in the preparation of this material is acknowledged, but is not to be construed as implying official approval by them of the conclusions presented.

This research was supported in part by a Research Scientist Award 5-KO5-MH-00245 from the National Institute of Mental Health to Dr Stunkard.

References

1. Bray GA, York DA: Genetically transmitted obesity in rodents. *Physiol Rev* 1971;51:598-646.
2. Davenport CB: *Body-build and its Inheritance*, publication 329. Washington, DC, Carnegie Institution, 1923.
3. Angel L: Constitution in female obesity. *Am J Phys Anthropol* 1939;7:443-471.
4. Garn SM, Clark DC: Trends in fatness and the origins of obesity. *Pediatrics* 1976;57:443-456.
5. Von Verscheuer O: Die vererbungsbiologische Zwillingsforschung. *Ergeb Inn Med Kinderheilkd* 1928;31:35-120.
6. Newman HH, Freeman FN, Holzinger KJ: *Twins: A Study of Heredity and Environment.* Chicago, University of Chicago Press, 1937.
7. Clark PJ: The heritability of certain anthropometric characters as ascertained from measurements of twins. *J Hum Genet* 1956;8:9-54.
8. Osborne RH, DeGeorge FV: Stature, weight and ponderal index, in *Genetic Basis of Morphological Variation.* Cambridge, Mass, Harvard University Press, 1959.
9. Shields J: *Monozygotic Twins Brought up Apart and Brought up Together.* New York, Oxford University Press Inc, 1962.
10. Brook CGD, Huntley RMC, Slack J: Influence of heredity and environment in determination of skinfold thickness in children. *Br Med J* 1975; 2:719-721.
11. Börjeson M: The aetiology of obesity in children. *Acta Paediatr Scand* 1976;65:279-287.
12. Medlund P, Cederlof R, Floderus-Myrrhed B, et al: A new Swedish twin registry. *Acta Med Scand* 1976;suppl 600, pp 5-107.
13. Feinleib M, Garrison RJ, Fabsitz R, et al: The NHLBI twin study of cardiovascular disease risk factors: Methodology and summary of results. *Am J Epidemiol* 1977;106:284-295.
14. Fabsitz R, Feinleib M, Hrubec Z: Weight changes in adult twins. *Acta Genet Med Gemellol* 1978;17:315-332.
15. Jablon S, Neel JV, Gershowitz H, et al: The NAS-NRC twin panel: Methods of construction of the panel, zygosity diagnosis, and proposed use. *Am J Hum Genet* 1967;19:133-161.
16. Hrubec Z, Neel JV: The National Academy of Sciences-National Research Council Twin Registry: Ten years of operation, in Nance WE (ed): *Progress in Clinical and Biological Research.* New York, Alan R Liss Inc, 1978, vol 24B, pp 153-172.
17. Keys A, Fidanza F, Karvonen MJ, et al: Indices of relative weight and obesity. *J Chronic Dis* 1972;25:329-343.
18. Fogarty International Center Conference on Obesity: Recommended weight in relation to height, in Bray GA (ed): *Obesity in Perspective,* publication (NIH) 75-708. US Dept of Health, Education, and Welfare, p 72.
19. Winer BJ: *Statistical Principles in Experimental Design,* ed 2. New York, McGraw-Hill International Book Co, 1971.
20. Falconer DS: *Introduction to Quantitative Genetics,* ed 2. New York, Ronald Press, 1981.
21. Loehlin JC, Nichols RC: *Heredity, Environment and Personality.* Austin, Tex, University of Texas Press, 1976.
22. Li CC: *First Course in Population Genetics.* Pacific Grove, Calif, Boxwood, 1976.
23. Kendler KS: Overview: A current perspective on twin studies of schizophrenia. *Am J Psychiatry* 1983;140:1413-1425.
24. Harvald B, Hauge M: Heredity factors elucidated by twin studies, in Neel JV (ed): *Genetics and the Epidemiology of Chronic Diseases,* Public Health Service publication 1163. US Dept of Health, Education, and Welfare, 1965.
25. Hrubec Z, Omenn GS: Evidence of genetic predisposition to alcoholic chirrhosis and psychosis: Twin concordances for alcoholism and its biological end points by zygosity among male veterans. *Alcoholism* 1981;5:207-215.
26. Hauge M, Harvald B, Fischer M, et al: The Danish twin register. *Acta Genet Med Gemellol* 1968;17:315-332.
27. Berg K: Twin research in coronary heart disease, in Gedda L, Parisi P, Nance WE (eds): *Twin Research: III. Epidemiological and Clinical Studies.* New York, Alan R. Liss Inc, 1981.
28. Holm NV: Studies of cancer etiology in the Danish twin population: I. Breast cancer, in Gedda L, Parisi P, Nance WE (eds): *Twin Research: III. Epidemiological and Clinical Studies.* New York, Alan R Liss Inc, 1981.
29. Longini IM, Higgins MW, Hinton PC, et al: Genetic and environmental sources of familial aggregation of body mass in Tecumseh, Michigan. *Human Biol* 1984;56:733-757.
30. Savard R, Bouchard C, Leblanc C, et al: Familial resemblance in fatness indicators. *Ann Hum Biol* 1983;10:111-118.
31. Fabsitz RR, Garrison RJ, Feinleib M, et al: A twin analysis of dietary intake: Evidence for a need to control for possible environmental differences in MZ and DZ twins. *Behav Genet* 1978; 8:15-25.
32. Munsinger H: The identical twin transfusion syndrome: A source of error in estimating IQ resemblance and heritability. *Ann Hum Genet* 1977;40:307-321.
33. Palta M, Prineas RJ, Berman R, et al: Comparison of self-reported and measured height and weight. *Am J Epidemiol* 1982;115:223-230.
34. Stunkard AJ, Sørensen TA, Hanis C, et al: An adoption study of human obesity. *N Engl J Med* 1986;314:193-198.

Downloaded From: by a Rijksuniversiteit Groningen User on 11/28/2017