The Genetics of Middle-Age Spread in Middle-Class Males

James C. Romeis,[1,2] Julia D. Grant,[2] Valerie S. Knopik,[3] Nancy L. Pedersen,[4] and Andrew C. Heath[2]

[1]Health Services Research, Department of Health Management and Policy, School of Public Health, Saint Louis University, St. Louis, Missouri,
   United States of America
[2]Missouri Alcohol Research Center, Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, United States
   of America
[3]Department of Community Health, Center for Alcohol and Addiction Studies, Brown University, Providence, Rhode Island, United States of America
[4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

This study provides findings to assist in identifying factors that contribute to the current clinical and public health debate of the *obesity epidemic*. The study examined the genetics of adult-onset weight change in middle-aged male–male twins controlling for weight in early adulthood, lifetime history of tobacco use and alcohol dependence, and aimed to estimate the proportion of genetic factors that influence weight change between early adulthood and middle age in white middle-class males. The study was a classic longitudinal twin design and used Body Mass Index (BMI) for three waves of data collection from the Vietnam Era Twin Registry — induction physicals (~ 1968), 1987 and 1990 — or periods corresponding between young adulthood and middle age. Univariate heritability estimates for BMI at all three data periods were conducted as well as a Cholesky longitudinal genetic analysis for weight change controlling for BMI at military induction, smoking and alcohol use. Frequency data indicated that the sample was on average classified as normal BMI in their 20s; but BMI gradually increased during the next twenty years. Univariate data for each data period indicated that additive genetic factors accounted for between 63% and 69% of total variance in BMI. The Cholesky longitudinal genetic analysis of BMI87 and BMI90, controlling for BMI at military induction, indicated that more than half of the change in BMI from early adulthood to middle age remains heritable. No shared environmental factors were identified, thus the remainder of the variance was accounted for by nonshared, or unique, environmental factors and error. The data analysis suggests that treatments and public health interventions need to recognize the magnitude of genetic factors if short-term and long-term interventions are to be effective.

This paper reports the results of a study designed to examine genetic and environmental factors in adult male weight gain, or what might also be described as *middle-age spread*. The popular press in the United States, as well as clinical and scientific journals, point to what is being labeled an *obesity epidemic* (Loehlin, 1992) with estimates of obesity for the US adult population indicating that approximately 34% are overweight and another 27% are classified as obese. The prevalence of obesity for adults has increased more than 75% since 1980. In children and adolescents the prevalence for being overweight has doubled since 1976 (Yanovski & Yanovski, 2002).

The magnitude of obesity and its change during the past few years is a serious concern for public health and policy officials because being overweight significantly increases the risk for Type 2 diabetes, cancer, hypertension, coronary artery disease, osteoarthritis and asthma (Kumanyika, 2001). Mortality related to obesity is estimated at 280,000 annually (Allison et al., 1999; Must et al., 1999; Peeters et al., 2003). In 1999, the costs for approved medications to treat obesity were US$321 million (Willhelm, 2000). Contrary to conventional wisdom, the effects of obesity on health and health costs may outrank both smoking and drinking (Sturm, 2002).

The most recent research trying to account for obesity generally points to two factors. The first is an energy imbalance resulting from an environment that promotes excessive dietary intake and a sedentary lifestyle, for example, food portion size increases, poor nutrition, advertising, fast food and more meals consumed away from home, variety, price, increased television viewing, and lack of exercise (French et al., 2001; Haire-Joshu & Nanney, 2002). The popular term *couch potato* did not emerge from a vacuum. As the physical environment becomes more *obesogenic*, average body weight is likely to continue to increase (Haire-Joshu & Nanney, 2002). The second factor is the genetic liability that accounts for variations in body

Received 18 August, 2004; accepted 19 September, 2004.

Address for correspondence: James C. Romeis, Department of Health Management and Policy, School of Public Health, Saint Louis University, St. Louis, MO 63104, USA. E-mail: romeisjc@slu.edu

596

Twin Research Volume 7 Number 6 pp. 596–602

https://doi.org/10.1375/twin.7.6.596 Published online by Cambridge University Press

fatness that exist among individuals in energy balance (Hill & Melanson, 1999). In this context, while genetic vulnerability has probably not changed during the past few years, environments have, thus allowing for the genetic vulnerability to be expressed as what appears to be an alarming rate of increase. Such an interpretation would be consistent with current literature in the field. An understanding of the way in which heritability influences body fatness may aid in understanding current findings that suggest weight control treatments achieve short- versus long-term efficacy (Jeffery et al., 2000).

The Genetics of Obesity

Body Mass Index (BMI = weight [kg]/height^2 [m]) is the most widely used measure of human weight. In the last decade there have been more than 11 review papers on the genetics of obesity (Maes et al., 1997). In general, twin and family studies estimate that one half to two thirds of the variance in BMI is heritable.

The National Academy of Sciences–National Research Council (NAS–NRC) sample is particularly relevant because it uses WWII male–male veteran twins measured initially at induction into military service (~ 20 years of age) and subsequently at ages 25 and 40 to 56. Because the severely obese (BMI > 35) are usually disqualified from military service, this population provides an opportunity to examine adult-onset weight change in nonextreme individuals passing into middle age and older. An important limitation is that the population excludes females. The univariate studies of BMI that include induction periods range in heritability between .62 and .82 (Fabstiz et al., 1978, 1992; Feinleib et al., 1977; Selby et al., 1991; Stunkard et al., 1986). Follow-up sample trends are not clear because of varying sample size and estimation methods, but heritability estimates of more than .50 are common. With the accumulation of the NAS–NRC data as well as other populations, Faith, Johnson and Allison (1997) argue that sufficient data have accumulated within classical univariate twin studies that research should pursue longitudinal and multivariate studies. Thus, this paper examines adult weight change and obesity from military induction to early middle age, controlling for alcohol and tobacco use, high-risk health behaviors associated with weight change (Eisen et al., 1993; Hellerstedt et al., 1990; Williamson et al., 1991).

Methods

Sample

The Vietnam Era Twin Registry (VETR) represents a community nonclinical sample of middle-aged, middle-class male–male twins who served in military service during the Vietnam War Era (1965 to 1975). The registry was constructed from computerized US Department of Defense files containing 7369 male–male twin pairs born between 1939 and 1957 where both siblings were on active duty during the

Vietnam Era. The sampling procedures and characteristics have been described in detail elsewhere (Eisen et al., 1987; Henderson et al., 1990). The sample sizes for this study varied by analysis. In the frequency data more than 8000 individuals were selected, reflecting individuals appearing in both the induction and the 1987 survey. For the cross-tabular analysis, the sample sizes varied by appearance in the corresponding waves and missing values.

Three periods of VETR data were used for this study. The first was associated with military induction record weight and height data (BMIMIL) and refers to the veterans' BMI at an age when they were on average in their 20s (average year of induction was 1968, SD = 2.3 years). The second period was associated with their weight and height obtained as part of the 1987 Survey of Health (BMI87). This mail and telephone survey was the first time the veterans were contacted and represents a period approximately 20 years after induction. The 1987 survey assessed psychological and physical health status as well as demographics and military service. Zygosity was determined by questionnaire and confirmed by blood group typing methodology (Eisen et al., 1987). The third period was associated with a 1990 follow-up telephone survey of the registry where weight and height was gathered (BMI90). The 1990 survey has approximately 2000 fewer respondents than the 1987 survey, but no more important demographic differences were noted, including zygosity (MZ = 55%, DZ = 45%). The overall response rate was 74.4% for those individuals participating in the 1987 survey.

Measures

BMI was used to classify individuals who were underweight (< 18.5), normal for height and weight (18.5 – < 25.0), individuals who were overweight (25.0 – < 30.0), obese (30.0 – < 35.0) and severely obese (> 35.0, e.g., 68' and > 239 lbs). BMI has recognized validity problems with classifying individuals who are very physically fit (because of muscle weight) as well as those who are characterized as having large bone structures. It has reasonable correspondence between independent clinical measurement and self-report. In this study BMI was treated as a continuous measure for the genetic analysis. Lifetime tobacco and alcohol dependence were measured with the Diagnostic Interview Schedule (Robins et al., 1989) during a 1992 survey of the registry and correspond to DSM III-R (Association, 1987) categories. These two measures are high-risk behaviors associated with weight change and obesity and were treated as statistical control variables. The 1992 survey did not assess BMI.

Analytical Strategy

As part of our descriptive analysis, we first conducted contingency table analyses for BMIMIL and BMI87 in the categories described above. Second, we evalu-

James C. Romeis, Julia D. Grant, Valerie S. Knopik, Nancy L. Pedersen, and Andrew C. Heath

ated heritability of BMI for each wave. The univariate analyses estimated the proportion of variance in BMIMIL, BMI87 and BMI90 that is attributed to genetic and environmental factors. The variance component analysis represents additive genetic factors, A, shared environmental factors, C, and nonshared or unique environmental factors and measurement error, E. Third, we assessed change in BMI using a Cholesky decomposition (Neal et al., 2002) analysis of BMI87 and BMI90, controlling for BMI at induction, or BMIMIL. Figure 1 depicts a BMI Cholesky longitudinal genetic analysis model path diagram representing the same factors (A, C, E) as in each of the univariate analyses while controlling for induction BMI. The Cholesky is typically used with longitudinal data to estimate genetic and environmental factors that are unique to a data period and those that are common to the previous data periods. For example, path a_{11} represents the estimate of genetic variance in BMI87, a_{21} represents the genetic variance in BMI90 that is shared with BMI87 and path a_{22} is the genetic variance unique to BMI90. The same path coefficient framework can be applied to C and E parameters. The BMIMIL path represents the control for BMI at military induction. We began testing models with the full ACE model then compared different models using maximum likelihood techniques until the most parsimonious best-fitting model was obtained. Finally we repeated the Cholesky analysis but included history of alcohol and nicotine dependence as co-variates, modeled as *definition* variables in Mx. We used both

SAS v8.02 (SAS, 2000) and Mx (Neal et al., 2002) for the biometrical genetic statistical analysis.

Results

Descriptive

Table 1 presents the 1987 frequency data for the demographic variables, tobacco and alcohol control variables, and BMI for the three data periods. In general, the sample was middle-aged, well educated, middle-class, married and employed. Smoking and alcohol dependence reasonably reflected the comparably aged US male population (CDC, 2002). Their average BMI and its standard deviation increased to an overweight classification from normal at induction. This gradual increase is better reflected in Table 2.

Cross-Tabulation

Table 2 is the cross classification of BMIMIL with BMI87. While not reported here, Table 2 is similar to cross classifications of BMIMIL with BMI90 and BMI87 with BMI90. There were three relationships that characterized the cross-tabular relationships. First, at induction almost three fourths of the sample's BMI was normal and 17% overweight. Second, twenty years later, 46% were normal and 44% overweight. On average, weight change increased for all periods with very little downward change. Third, at induction approximately 2.5% were obese or severely obese reflecting the usual exclusion of individuals who were obese at induction. This compared to approximately 12% who were obese in 1990, or a fivefold change 20 years later.
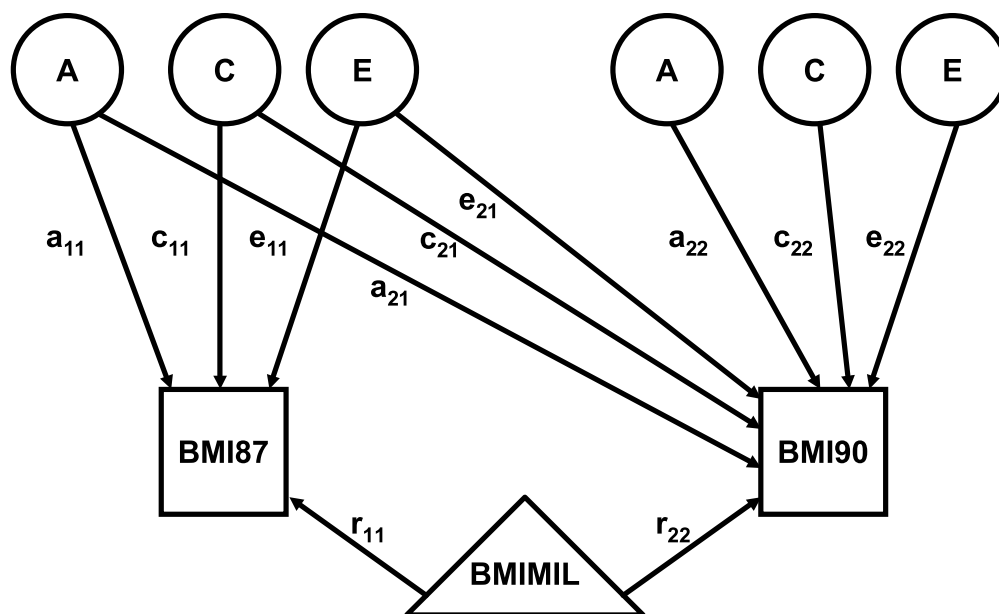

Figure 1

BMI Cholesky model

A = additive genetic, C = shared environment, E = Nonshared environment & error, BMIMIL = control, or definition variable

Table 1

Sample and Variable Frequency Distributions (*N* = 8074 Individuals)

Age		Education (years)	
• 30–42	= 74%	• 6–12	= 36%
• 43–51	= 26%	• 13–16	= 38%
		• 17–20+	= 26%

Gross household income		Marital status	
• < $9999	5.8%	• Never married	= 7%
• $10,000–19,999	13.2%	• Married	= 85%
• $20,000–49,999	63.1%	• Wid/ sep/ div	= 8%
• > $50,000	17.9%		

Employment status		Race	
• Full time	= 92%	• Caucasian, non-Hispanic	= 90.4%
• Part time	= 2%	• African-American	= 4.9%
• Other	= 6	• Other	= 4.7%

Smoking status			
• Never smoked= 30%		• Nicotine dependence	
		— No	= 52%
		— Mild	= 30%
		— Mod.	= 17%
		— Severe	= 1%

Alcohol use, abuse, dependence			
• No, abuse	= 65%	• Dependence (20% of dependence = severe)	= 35%

BMIMIL	av. = 22.5, *SD* = 3.0
BMI87	av. = 25.7, *SD* = 3.4
BMI90	av. = 26.0, *SD* = 3.6

Heritability

Table 3A shows the results from the univariate analyses for the continuous measures of BMI for each data period expressed as bar charts rather than path diagrams. Each bar shows the total variance in BMI by year and the proportion of variance attributed to A, C and E. The proportion of variance attributed to addi-

tive genetic factors, A, ranged between 62% and 69%. Shared-environmental factors, C, accounted for 14% of the variance at early adulthood (BMIMIL) but decreased to a negligible amount in middle age or the other two measurement periods. Although expected, a shared environment effect is not usually reported in genetic studies of BMI but would seem to correspond to the importance of one's family of origin for males entering early adulthood. What is clear for these data are that variance in BMI increased over time, for example, an increase of 43.5% to BMI90 from BMIMIL. In the univariate comparisons the influence of additive genetic factors accounted for about two thirds of the variance and increased slightly across the periods. The shared environmental influence in early adulthood decreased to a negligible amount in 1990. Finally, there was a concomitant increase in the role of the nonshared environmental influence and error.

The Cholesky analysis extended the cross-sectional univariate analysis by assessing the importance of genetic and environmental factors for BMI in 1987 and BMI in 1990 controlling for BMI at military induction. By using BMIMIL as a control variable, we were estimating the proportions of variance of the residual variance (after accounting for BMIMIL) due to A, C and E. Table 3B indicates the best-fitting model. When controlling for BMIMIL, additive genetic factors accounted for 53% of the variance in BMI87 with 47% attributed to nonshared, or unique, environmental factors and error. For BMI in 1990, 3% of the variance was attributed to additive genetic factors unique to 1990 and 50% additive genetic factors were shared with genetic factors attributed to 1987. Nonshared environmental factors were divided between the two periods; 20% were shared with the 1987 period and 26% were unique to 1990. When alcohol and nicotine dependence were included as additional covariates, no appreciable difference was
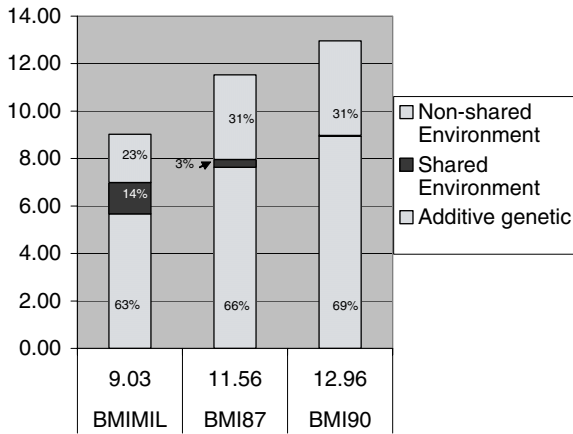
Table 2

Cross-Tabulation Between Induction BMI and 1987 Survey BMI

| *N* (%)	'87 Under	Normal	Over	Obese	Severely obese	Total
MIL under	13	355	50	2	0	420
	(3.1)	(84.5)	(11.9)	(0.5)	(0.0)	(5.3)
Normal	22	3089	2547	227	25	5910
	(0.4)	(52.3)	(43.1)	(3.8)	(0.4)	(74.8)
Over	2	183	820	314	57	1376
	(0.2)	(13.3)	(59.6)	(22.8)	(4.1)	(17.4)
Obese	0	15	57	71	41	184
	(0.0)	(8.6)	(30.9)	(38.6)	(22.3)	(2.3)
Severely obese	0	1	6	1	1	9
	(0.0)	(11.1)	(66.7)	(11.1)	(11.1)	(0.1)
Total	37	3643	3480	615	124	7899
	(0.5)	(46.1)	(44.1)	(7.8)	(1.6)	100

Table 3A

Phenotypic Variance and BMI Univariate Heritability for Induction and Follow-Up Survey Periods

Note: Value above label is total phenotypic variance for each data period.

Table 3B

Phenotypic Variance and Longitudinal BMI Variance Decomposition for 1987 and 1990 Survey Periods, Controlling for Induction BMI
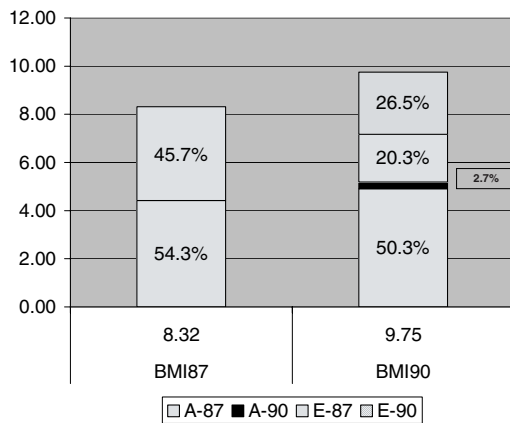
Note: Value above label is total phenotypic variance controlling for BMIMIL.
$-2\,LL = 71928.038$, $df = 16082$

noted. No shared environmental factors were significantly related to BMI in either period.

Discussion and Conclusions

Obesity has been characterized as a modern epidemic, with approximately one quarter of the adult population considered obese, and accounting for US$92.6B of total annual medical expenditures (Finkelstein et al., 2003). This longitudinal study is designed to assess the importance of genetic and environmental factors for 20-year weight change and obesity in a sample of middle-class, middle-aged male–male Caucasian twins. The design controls for weight

assessed in early adulthood and lifetime history of alcohol and tobacco dependence, known co-variates of obesity and weight change. In early adulthood, three fourths of the sample are classified as normal weight, 17% are overweight and 2.5% are obese and severely obese. Twenty years later, approximately 45% are classified as normal, 45% are overweight and 9% to 12% are classified as obese or severely obese. Weight appears to increase gradually, with little evidence of cross-category decreases. The cross-sectional heritability analysis indicates that approximately two thirds of BMI at the three periods is attributed to additive genetic factors. The importance of early-adult shared-environmental factors declines as the sample ages and nonshared environmental factors and error increase. Further, inspection of the variance estimates indicates that genetic influences are not becoming more important, but rather that individual specific environmental variation is increasing across this 20-year period.

The longitudinal Cholesky analysis indicates that, controlling for early adulthood BMI and high-risk health behaviors, genetic factors account for more than 50% of variance in BMI. Nonshared or unique environment, and measurement error accounts for the remainder of the total phenotypic variance. This suggests that while BMI in early adulthood is influenced by genetic liabilities, they are not deterministic but are influences that need to be accounted for if both short- and long-term treatments or public health interventions are to be effective. The data also suggest that little nonshared environment (and error variance) is transmitted from 1987 to 1990 measures of BMI, thus vigilance in weight control should be maintained or buying larger pants or loosening one's belt will have to be considered. With the magnitude of genetic liability, it seems reasonable to explore incentives for weight loss that build on current cognitive and education interventions but offset the environmental inducements associated with weight gain. Finally, the lack of statistical importance attributed to nicotine and alcohol use on weight change is unclear and requires further study. This could be due to specification problems, assessment times, or these variables may act as short-term influences and thus their affects are not captured here.

The most obvious study limitation is that the sample is limited to males and does not include analysis of diet and exercise. We do, however, respond to arguments in the field to put more behavior into longitudinal analysis of the genetics of weight change and adult-onset obesity.

References

Allison, D., Fountaine, K., Manson, J., Stevens, J., & Van Itallie, T. (1999). Annual deaths attributed to obesity in the United States. *Journal of American Medical Association, 282,* 1530–1538.

Association, A. P. (1987). *DSM-III-R. Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: American Psychiatric Association.

Centers for Disease Control (CDC). (2002). *Advance Data #330. Body weight status of adults: 1997–1998.* Atlanta, GA: Author.

Eisen, S., Lyons, M. J., Goldberg, J., & True, W. R. (1993). The impact of cigarette and alcohol consumption on weight and obesity. An analysis of 1911 monozygotic male twin pairs. *Archives of Internal Medicine, 153,* 2457–2463.

Eisen, S., True, W. R., Goldberg, J., Henderson, W., & Robinette, C. D. (1987). The Vietnam Era Twin (VET) Registry: Method of construction. *Acta Geneticae Medicae et Gemellologiae, 36,* 61–66.

Fabsitz, R. R., Carmelli, D., & Hewitt, J. K. (1992). Evidence for independent genetic influences on obesity in middle age. *International Journal of Obesity, 16,* 657–666.

Fabsitz, R. R., Garrision, R. J., Feinleib, M., & Hjortland, M. (1978). A twin analysis of dietary intake: Evidence for a need to control for possible environmental differences in MZ and DZ twins. *Behavior Genetics, 8,* 15–25.

Faith, M., Johnson, S. L., & Allison, D. B. (1997). Putting the behavior into the behavior genetics of obesity. *Behavior Genetics, 27,* 423–439.

Feinleib, M., Garrison, R. J., Fabsitz, R. R., Christian, J. C., Hrubec, Z., Borhani, N. O., Kannel, W. B., Rosenman, R., Schwartrz, J. T., & Wagner, J. O. (1977). The NHLBI twin study of cardiovascular disease risk factors: Methodology and summary of results. *American Journal of Epidemiology, 106,* 284–295.

Finkelstein, E., Fiebelkorn, I. C., & Wang, G. (2003). National medical spending attributable to overweight and obesity: How much, and who's paying? *Health Affairs*(Suppl. W3), 219–226.

French, S. A, Story, M., & Jeffery, R. W. (2001). Environmental influences on eating and physical activity. *Annual Review of Public Health, 22,* 309–335.

Haire-Joshu, D., & Nanney, M. S. (2002). Prevention of overweight and obesity in children: Influences on the food environment. *Diabetes Educator, 28,* 415–423.

Hellerstedt, W., Jeffery, R. W., & Murray, D. M. (1990). The association between alcohol intake and adiposity in the general population. *American Journal of Epidemiology, 132,* 594–611.

Henderson, W., Eisen, S., Goldberg, J., True, W. R., Barnes, J. E., & Vitek, M. E. (1990). The Vietnam Era Twin Registry: A resource for medical research. *Public Health Reports, 105,* 368–373.

Hill, J. O., & Melanson, E. L. (1999). Overview of the determinants of overweight and obesity: Current evidence and research issues. *Medicine and Science in Sports and Exercise, 31,* S515–S521.

Jeffery, R., Drewnowski, A., Epstein, L. H., Stunkard, A. J., Wilson, G. T., Wing, R. R., & Hill, D. R. (2000). Long-term maintenance of weight loss: Current status. *Health Psychology, 19*(1 Suppl. January), 5–16.

Kumanyika, S. K. (2001). Minisymposium on obesity: Overview and some strategic considerations. *Annual Review of Public Health, 22,* 293–308.

Loehlin, J. D. (1992). *Genes and environment in personality development.* Newberry Park, CA: Sage.

Maes, H., Neale, M. C., & Eaves, L. J. (1997). Genetic and environmental factors in relative body weight and human adiposity. *Behavior Genetics, 27,* 325–439.

Must, A., Spadano, J., Coakley, E., Field, A., & Dietz, W. (1999). The disease burden associated overweight and obesity. *Journal of American Medical Association, 282,* 1523–1529.

Neal, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2002). *Mx: Statistical modeling.* (6th ed.). Richmond, VA: Department of Psychiatry, Virginia Commonwealth University.

Peeters, A., Barendregt, J., Willekens, F., Mackenback, J., Al Mamun, A., & Bonneux, L. (2003). Obesity in adulthood and its consequences for life expectancy: A life-table analysis. *Annals of Internal Medicine, 138,* 24–32.

Robins, L. N., Helzer, J. E., Cottler, L., & Goldring, E. (1989). *Diagnostic interview schedule.* (Version III revised ed.). Rockville, MD: National Institute of Mental Health.

SAS. (2001). *SAS/STAT user's guide (Version 8.02).* Cary, NC: SAS Institute.

Selby, J. V., Reed, T., Newman, B., Fabsitz, R. R., & Carmelli, D. (1991). Effects of selective return on estimates of heritability for body mass index in the National Heart Lung and Blood Institute Twin Study. *Genetic Epidemiology, 8,* 371–380.

Stunkard, A. J., Foch, T. T., & Hrubec, Z. (1986). A twin study of human obesity. *Journal of American Medical Association, 256,* 193–198.

James C. Romeis, Julia D. Grant, Valerie S. Knopik, Nancy L. Pedersen, and Andrew C. Heath

Sturm, R. (2002). The effects of obesity, smoking and drinking on medical problems and costs. *Health Affairs, 21,* 245–252.

Willhelm, C. (2000). Growing the market for anti-obesity drugs. *Chemical Market Reporter, May 15,* FR23–FR24.

Williamson, D., Madans, J., Anda, R. F., Kleinman, J. C., Giovino, G. A., & Byers, T. (1991). Smoking cessation and severity of weight gain in a national cohort. *New England Journal of Medicine, 324,* 739–745.

Yanovski, S., & Yanovski, J. (2002). Obesity. *New England Journal of Medicine, 346,* 591–602.