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Genetics of Body Mass Stability and Risk for Chronic Disease: A 28-Year Longitudinal Study

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We examined the contributions of genetic and environmental factors to body mass index (BMI) over approximately 28 years. Participants were 693 male, predominantly middle-class, twins (355 monozygotic, 338 dizygotic) from the Vietnam Era Twin Registry. The phenotypic correlation between age 20 and age 48 BMI was 0.52; the genetic correlation was 0.60. Most of the remaining variance at both times was accounted for by nonshared environmental factors. Since genetic factors are not perfectly correlated, this indicates that other genes affect BMI at one or both time points, leaving room for further exploration of the genetics of body mass stability. Mean BMI increased significantly from 22.7 (normal) to 27.8 (overweight). Overweight BMI at age 20 predicted midlife adult onset diabetes (adjusted odds ratio = 4.62, 95% CI 1.91 to 11.18), but not hypertension. Depending on one's vantage point, the results indicate elements of both stability and change in BMI. Very similar phenotypic and genetic correlations were observed over a similar time period in a WW II twin sample, but without the substantial mean increase in BMI. It seems unlikely that different genes influence BMI in the two cohorts. Therefore, we argue that nonshared environmental factors are probably primarily responsible for the secular increase in midlife BMI. Our results also provide prospective evidence that early excess BMI may have serious long-term health consequences, and that this risk is not limited to minorities or adults of lower socioeconomic status.

Recent estimates suggest that 61 per cent of American adults are overweight or obese (Sturm, 2003; Wyatt, 2003). The elevated health risks and mortality associated with a high body mass index (BMI: body weight corrected for height) are well-established, particularly among middle-aged and older adults (Flegal et al., 2005; Gregg et al., 2005; Hu et al., 2005; McGee & The Diverse Populations Collaboration, 2005). Obesity is recognized as a major behavioral risk factor for chronic health conditions such as cardiovascular disease, diabetes, elevated triglycerides, hypertension and elevated systolic blood pressure, with the equivalent effect of 20 years aging on health outcomes (Gregg et al., 2005; Sturm, 2002). Epidemiologic data show the average BMI of Americans rising steadily from adolescence to middle age, across sex and ethnic groups (Sheehan et al., 2003). Thus, examination of the extent to which genetic factors contribute to BMI over time and the influence of early life BMI on chronic disease is important for multiple reasons.

Although population rates of obesity are rising, the heritability of BMI remains relatively stable. There is strong support for the influence of genes on single-time point BMI, with reports of heritability ranging from .45 to .87 (Jacobson & Rowe, 1998; Keller et al., 2003; Loos & Bouchard, 2003; Maes et al., 1997; Romeis et al., 2004). Overall, genetic factors appear to exert stronger influences than environmental factors on BMI at any given time (Hanisch et al., 2004). Fewer researchers have examined the genetic contribution to BMI over time. Stunkard et al. examined BMI concordance rates in World War II (WWII) twin veterans at the time of military induction (average age 20) and 25 years later (age range 40 to 50). Concordance rates for MZ

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twins were significantly higher than for DZ twins at both times. Using intraclass correlations, heritability for BMI was estimated at .77 and .84 at military induction and the 25-year follow-up, respectively, indicating significant genetic influences at both times. The phenotypic correlation in BMI over time was .54. Using path analyses, the genetic correlation for BMI over time was estimated at .69, indicating substantial stability in the genetic factors that influence BMI (Stunkard et al., 1986). Fabsitz et al. examined maximum lifetime BMI, and trend (slope) of BMI at mean ages 20, 48, 57, and 63 in the same sample of twin veterans. Heritability of maximum BMI was estimated at .74 and heritability of the trend in BMI change was .70 (Fabsitz et al., 1994; Stunkard et al., 1986). Variability of BMI at each time was also examined but showed no genetic variance.

Romeis et al. (2004) examined heritability of self-report BMI in Vietnam era veteran twins across five years, controlling for BMI at military induction. Height and weight of twins were assessed at military induction (average age 20), then surveyed in 1987 (ages in mid-30s) and 1990 (ages in early 40s). Heritability of BMI was .63, .66, and .69 at induction, 1987, and 1990, respectively. Decomposition of the longitudinal BMI variance from 1987 to 1990 (after controlling for induction BMI) indicated that 50.3% of the variance in 1990 BMI was due to additive genetic factors shared with BMI in 1987; 2.7% of the genetic variance was unique to 1990 BMI (Romeis et al., 2004). In contrast, the influence of nonshared environmental factors in 1990 was fairly evenly divided between factors shared with 1987 BMI (20.3%) and environmental factors unique to 1990 BMI (26.5%). However, one study of Finnish adult twin pairs across six years indicated that, although the genetic component of BMI was sizable and stable, weight change was determined primarily by environmental effects rather then genetic factors (Korkeila et al., 1995). Finally, a longitudinal family study examined BMI through frequent assessments across 20 years; measures included average, maximum, variation, and change in BMI. Heritability estimates for average BMI and maximum BMI were .37 and .40, respectively. Analyses of the BMI average annual slope across 20 years found low heritability (.13; Coady et al., 2002). Methodological differences among these studies such as age, gender, developmental stage at time of measurement, cohort differences, duration of study, spacing of assessments, methodology (twin vs. family), sample size, covariates, and whether analyses were of variability or change, may explain the inconsistencies.

This study examined the contribution of genetic and environmental factors to BMI at two important developmental, transitional periods in the same sample: average age 19.8 (*SD* = 1.63; range 16–27) and 47.8 (*SD* = 3.3; range 41–58). We then estimated the degree to which genes versus environments account for stability in BMI over time (i.e., genetic contribution to covariance). Third, we also evaluated the extent of overlap of genes that contribute to *variation* in BMI across these 28 years (i.e., the genetic correlation). These time points are biologically meaningful because men tend to achieve adult height around age 20; height then remains stable until after age 50. Weight, which increases rapidly during adolescence, tends to increase at a slower pace until the mid-50s (National Health and Nutrition Examination Survey [NHANES] III, 1999–2004).

In addition, in the United States (U.S.), rates of self-reported chronic diseases commonly associated with BMI increase substantially between ages 20 and 48 (Centers for Disease Control and Prevention; NHANES III, 1999–2004). Among U.S. men, self-reported rates of diabetes increase from 3.6% at ages 20 to 44 to 10.3% among adult men ages 45 to 64, as does hypertension (12.3% in 20–44 year olds to 29.8% in 45–64 year olds). After age 65, the prevalence of diabetes is 16.9%, and the prevalence of hypertension is 44.6% among men (NHANES III, 1999–2004). Thus, both time points in this study involve important transition points. Age 20 coincides with the transition to adulthood, when adult height stabilizes, so increases in body weight contribute solely to increases in BMI. Age 48 falls at a point in middle age when substantive health-related changes appear. Thus, as our final research question, given current concerns about the long-term impact of excessive body mass in adolescents, we examine the long-term effect of early adult BMI on the development of two chronic medical problems by midlife: adult-onset diabetes and hypertension (Haffner, 2006; Lee et al., 2006). A better understanding of the genetic and environmental influences on BMI during this period may shed light on the contributions of BMI to disease processes such as obesity, diabetes, and hypertension.

Materials and Methods

Participants and Procedures

Participants were enrolled from the Vietnam Era Twin Registry (VETR), a national registry of several thousand male twin pairs in which both members served in the military between 1965 and 1975. Questionnaire and blood group methods determined zygosity with 95% accuracy. A complete description of the registry construction has been previously reported (Eisen et al., 1987).

Between 1996 and 2001, when the twins average age was 48 years, a follow-up was conducted which included 345 twin pairs and 3 unpaired twins (total *N* = 693 individuals), randomly selected from a larger random sample of more than 3300 pairs surveyed in a previous study (Tsuang et al., 2001). Participants flew in from around the country for a day-long assessment either at the University of California Davis School of Medicine, Sacramento, CA or Harvard

Medical School, Boston, MA: see Crider et al. for details of the assessment (Crider et al., 2004). Assessments included: demographic measures, detailed medical history taking, measured height and weight, two blood pressure measurements, personality measures, and a cognitive battery. Institutional review boards at both sites approved the study and all participants gave written informed consent. The VETR provided height and weight measurements from the time that the twins were inducted into the military (average age 20); these data were obtained from participants' military record data. For convenience, we refer to the two study time points as age 20 and 48 even though these technically refer to the average age at each time.

Body Mass Index (BMI)

BMI (weight in kg/height in meters^2) was calculated using measured height and weight for all except 43 twins (6.2 %), for whom only self-reported weight was available at age 48. The sample consisted of 693 individual twins (355 MZ, 338 DZ). Two twins were missing BMI data at both time points, and were not included in the analyses. Most twins (N = 634, 91.5%) had BMI data at both time points. A small number of twins (N = 11, 1.6%) were missing BMI at age 48, and 46 twins (6.6%) did not have BMI data at age 20. All twins with at least some non-missing data were included in the analyses. The final sample consisted of 296 twin pairs (149 MZ, 147 DZ) with complete data from both twins (85.1% of the twin pair sample), 38 pairs (20 MZ, 18 DZ) with complete data from one twin but partially missing data from the second twin, 9 pairs (6 MZ, 3 DZ) with partially missing data from both twins, and 5 pairs (4 MZ and 1 DZ) with data from only one twin.

For genetic analyses, BMI was used as a continuous measure. For descriptive purposes, BMI was categorized into clinically meaningful groupings using National Heart, Lung, and Blood Institute (NHLBI) guidelines. Low BMI was defined as more than 16 and less than 18.5, normal BMI as equal to, or greater than 18.5 and less than 25, overweight BMI was equal to, or greater than 25 and less than 30, and obese was BMI equal to, or greater than 30. After inspection of the frequencies, these groupings were further collapsed to normal BMI ($>$ 16 to $<$ 25) and overweight ($\geq$ 25) for the BMI health risk analyses. At age 20, only 30 participants had low BMI and only 10 were obese.

Health Indicators at Midlife

At age 48, morning and afternoon blood pressure readings were taken twice on the day of testing using a standard/automated mercury sphygmomanometer while the subjects were seated. Morning and afternoon readings were acquired twice, 1 minute apart. The four systolic and four diastolic readings were averaged and characterized as normal or hypertensive according to NHLBI criteria (Chobanian et al., 2003). These criteria define hypertension, or high blood pressure, as systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90 mmHg. Participants were also asked if they had ever been told by a doctor that they had high blood pressure, if they had seen a doctor for high blood pressure in the past five years, and what medications, if any, they were taking for high blood pressure. Hypertension (yes/no) was defined as either: (a) blood pressure greater than or equal to 140/90 mmHg or (b) taking antihypertensive medication (regardless of blood pressure reading). Other common indicators of cardiovascular disease occurred too infrequently to examine; blood chemistries were not obtained.

At age 48, participants were also asked if they had ever been told by a doctor that they had diabetes, the age of onset, and whether it was controlled by medication and/or insulin. Adult onset diabetes was coded as present if a participant indicated he had been diagnosed with diabetes as an adult and was taking either medication or insulin for diabetes. Comparisons of dates of military induction with self-report of age of onset indicated that no participants reported they had diabetes at the time of induction. Six hundred and forty-five twins had both age 20 BMI data and age 48 health data; three twins who reported diabetes at age 48 and seven twins with hypertension at age 48 did not have BMI data at age 20. 671 individual twins had both health and BMI data at age 48.

Statistical Analyses

Genetic analyses were performed using Mx statistical modeling software fit to raw data (Neale et al., 2002). To model genetic and environmental influences on variation in, and covariation across, BMI at the two time points, we fit a bivariate Cholesky model (Neale & Cardon, 1992) to our continuous measures of BMI. For ease of interpretation, the bivariate Cholesky model can be reparameterized as a Correlated Factors model (Loehlin, 1992; Neale & Cardon, 1992), shown in Figure 1 (for simplicity, only one twin is shown in the diagram). Like the Cholesky model, the Correlated Factors model uses 9 parameters to capture the variation in, and covariance across, BMI measures. The Cholesky and Correlated Factors Models further yield identical fits. We use the Cholesky model in our primary analyses simply for technical reasons concerning positive–definiteness of our matrices, and because of its ease in testing specific submodels. However, results are presented in the Correlated Factors framework.

The parameters depicted in the Correlated Factors model show the estimated effects of genetic (a^2), common environmental (c^2), and nonshared environmental (e^2) influences on BMI at each time point, as well as the genetic (R_a), common environmental (R_c), and nonshared environmental (R_e) correlations across BMI, which indicate the degree to which genetic and environmental influences on BMI overlap across the

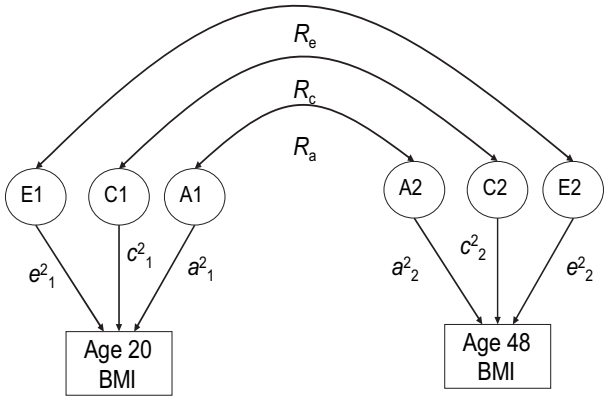

Figure 1

Correlated factors model.

Note: This figure (which for simplicity, is shown for only one twin), shows the contributions of additive genetic (A), common or shared environment (C), and nonshared (E) factors account for variation in age 20 (A1,C1,E1)and age 48 (A2,C2,E2) body mass index (BMI). These factors are allowed to correlate: correlations between genetic factors (Ra), common environmental factors (Rc), and shared environmental factors (Re). In the Correlated Factors Model, the heritability of age 20 BMI is $a1^2$; the heritability of age 48 BMI is $a2^2$. Corresponding estimates of shared environmental ($c1^2$ and $c2^2$) and nonshared environmental ($e1^2$ and $e2^2$) estimates were obtained.

two age periods. In this figure, one can clearly see that different sets of A, C, and E factors account for variation in age 20 (through paths a_1, c_1, and e_1) and age 48 (through paths a_2, c_2, and e_2) BMI, and that these factors are further allowed to correlate (i.e., R_a, R_c, and R_e). In the Correlated Factors Model, the heritability of age 20 BMI is simply a_1^2. Similarly, the heritability of age 48 BMI is a_2^2. Corresponding estimates of shared environmental (c_1^2 and c_2^2) and nonshared environmental (e_1^2 and e_2^2) estimates are also obtained.

In addition to estimating the relative importance of genetic factors on variation in BMI in young adulthood and midlife, our primary analyses concern two related questions concerning genetic and environmental influences on BMI over time. First, we are interested in the extent to which genetic factors account for stability in BMI over time. In the Correlated Factors model, the phenotypic correlation (R_p) is estimated by summing $a_1 * R_a * a_2 + c_1 * R_c * c_2 + e_1 * R_e * e_2$. Thus, the stability in BMI as measured by the phenotypic correlation can be broken down into stability due to genetic, shared environmental, and nonshared environmental factors. For example, the extent to which genetic factors account for the phenotypic stability can be calculated by dividing ($a_1 * R_a * a_2$) by R_p. Second, we can also examine *the stability of genetic and environmental influence on BMI over time* by examining the 95% confidence intervals (CIs) around our estimates of *Ra*, *Rc*, and *Re* in the Correlated Factors Model (see Figure 1). For example, if *Ra* = 1.0, this indicates that the genetic factors influencing variation in Time 1 and Time 2 BMI are completely overlapping. If *Ra* = 0.0, this indicates that entirely separate sets of genetic factors influence BMI at the two different time points. Similar logic is applied to the estimates of *Rc* (for overlap of shared environmental factors) and *Re* (for overlap of nonshared environmental factors).

Mx uses full information maximum likelihood to estimate model parameters that yield a minus two log likelihood (–2LL) fit function. We use goodness-of-fit statistics to evaluate the fit of our various models. For the overall fit of the full bivariate Cholesky model, the difference between the fit functions (compared to a *saturated model* which perfectly recaptures mean levels, variance, and covariance of the observed data) is distributed as chi-square with degrees of freedom equal to the difference in the number of parameters estimated between the models. Goodness-of-fit was assessed by this discrepancy function ($\Delta\chi^2$ statistic). For nested models, we compare the –2LL statistic from our nested submodel to that of our comparison model using the $\Delta\chi^2$ statistic. Significant $\Delta\chi^2$ values indicated that the model we are testing fit significantly *more poorly* than the comparison model. We also examined Akaike's Information Criteria (AIC) for each model (Akaike, 1987). The AIC is a statistic that balances both goodness-of-fit and parsimony. Models with more negative AIC values are considered the best-fitting models.

Descriptive statistics and analysis of the phenotypic association of BMI and health relationships were conducted using SPSS and SAS statistical software (SAS; SPSS). Logistic regression was used to calculate odds ratios for the association of BMI status (i.e., normal versus overweight) at each time with midlife diabetes and hypertension. Regression analyses were performed using the SAS procedure 'Surveylogistic' in order to adjust for the effect of twin pair clustering (SAS). Logistic regressions were conducted separately for BMI at age 20 and age 48, with statistical adjustment for selected covariates: age (less than or equal to 48 years old vs. older than 48), ethnicity (white vs. other), education (high school vs. more than high school), and twin pair clustering. Age was controlled for at the age 48 data collection because the likelihood of developing diabetes increases with age (NHANES III, 1999–2004).

Results

Descriptive Statistics

Table 1 shows the demographic characteristics of the total sample of 691 twins. At midlife, participants were predominantly middle-class, moderately well-educated, and married; 92% worked full-time. The average age at military induction was 20, average age at midlife testing was 48. Comparisons of MZ and DZ twins on demographic measures yielded no significant differences, and neither parental (r = –.06, –.05 *ns*; MZ, DZ respectively) nor the participants' socioeconomic status (r = .02, –.03 *ns*) was associated with BMI at either time.

Table 1

Sample Demographics at Age 48 ($N = 691$)

Age	47.8 *SD* 3.3 (Range 41–58)
Ethnicity	
Caucasian	92.2%
African–American	5.5%
Hispanic	1.9%
Other	0.4%
Education	
Completed high school	96.7%
Completed college	33.0%
Marital status	
Married	79.1 %
Divorced	12.1%
Other	8.8%
Employment	
Full-time	92.2%
Part-time	1.6%
Other (e.g., unemployed disability, retired)	6.2%
Occupation	
Service/manual labor	33.5%
Clerical/semi-professional	24.4%
Professional	41.1%
Median Income (USD)	$60,000–$70,000

Average BMI increased significantly from age 20 to age 48 from a mean of 22.7 (SD = 3.0) to 27.8 (SD = 4.2). A model that equated BMI at each time point resulted in a highly significant difference in fit compared to a model where BMI was estimated separately at each time point ($\Delta\chi^2_1 = 465.82$; $p < .001$). However, there were no significant differences in mean level BMI at either time point across twins within pairs ($\Delta\chi^2_4 = 6.27$; $p = .18$; AIC = –4.86), or across zygosity ($\Delta\chi^2_2 = 1.50$; $p = .47$; AIC = –7.36). Thus, these means were equated in all subsequent structural equation modeling analyses.

Genetic and Environmental Influences on BMI

To address our primary research questions, we fit the full bivariate Cholesky model to the observed raw data. Comparison of this full model to the saturated model revealed an overall acceptable fit to the data ($\Delta\chi^2_{17} = 26.64$; $p = .60$; AIC = –7.36). A model dropping all A effects did not fit the data well ($\Delta\chi^2_3 = 113.42$; $p < .001$; AIC = +100.06), indicating a significant influence of genetic factors at one or both time points. In contrast, dropping all C effects from the model did not result in a significant deterioration in fit compared to the full ACE model ($\Delta\chi^2_3 = 0.73$; $p = .87$; AIC = –12.64). Nonetheless, because estimates of shared environmental effects were non-zero, we include them in our model in order to avoid artificially over-stating the importance of genetic factors.

The results from the full model are presented in Figure 2. Consistent with previous reports, genetic factors were the primary source of variation in BMI at age 20 and age 48 (heritability = 76% and 59%, respectively). Nonshared environmental factors also contributed significantly to variation at each time, accounting for 17% and 34% of the variation in BMI at ages 20 and 48, respectively. Shared environmental influences accounted for a negligible (7%, *ns*) amount of variance of BMI at each time point.

We then examined the extent to which genetic versus environmental factors are responsible for covariance in BMI over time; that is, what accounts for the correlation in BMI across time. The estimated phenotypic correlation between BMI at age 20 and BMI at age 48 was .52, indicating considerable stability in BMI over time. Based on the estimates from the model, genetic factors accounted for 76% of the correlation (95% CI .43 to .96), shared environmental factors accounted for 14% (95% CI .00 to .44), and nonshared environmental factors accounted for the remaining 10% (95% CI .03 to .19).

The third research question examined the extent of overlap of genes that contribute to *variation* in BMI across these 28 years (i.e., the genetic correlation). As can be seen in Figure 2, in the full correlated factors model, the genetic correlation of the overlap between age 20 and age 48 BMI was estimated at .60 (95% CI .44 to .76). This suggests that some, but not all of the genetic influence on BMI is accounted for by the same genes over time. Similarly, the nonshared environmental correlation (.22, 95% CI .07 to .36) also indicates a modest overlap of nonshared environmental factors over time. The shared environmental correlation was estimated at 1.0, suggesting that the shared environmental influences that impact on variation in BMI at each time point are completely overlapping. However, because the shared environmental influences on BMI at both time points were so negligible, the 95% CIs indicate that the shared environmental influences may also be entirely distinct at the two time points (i.e., the 95% CI includes 0).

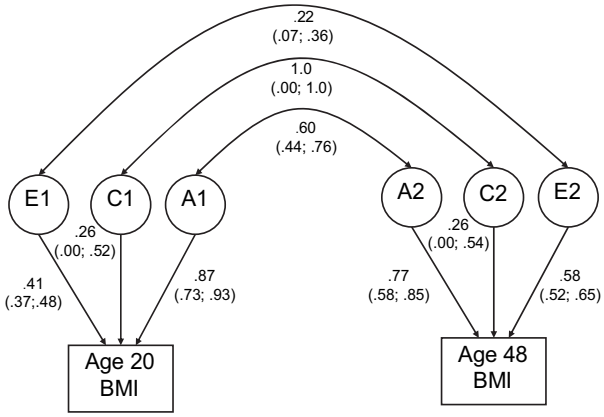

Figure 2

Standardized parameter estimates from full model.

Note: This model shows the contributions of additive genetic factors (A), shared environment (C), and nonshared environment (E) to BMI at age 20 (A1,C1,E1 respectively) and age 48 (A2, C2, E2), and the overlap of genetic (R_a), shared environmental (R_c) and nonshared environmental (R_e) factors across time points.

Table 2

Prevalence Rates — *N* Cases per BMI Group (per cent) — of Health Indicators at Age 48 and BMI Status at Age 20

	Body mass group at age 20	
	Normal BMI (*N* = 511)	Overweight (*N* = 134)
Diabetes Age 48 (*N* = 29)	14 (2.7%)	15 (11.2%)
Hypertension Age 48 (*N* = 244)	191 (38.1%)	53 (39.9%)

Note: BMI = Body Mass Index. Prevalence rates = disease frequency in each BMI group. Normal BMI ≥ 18.5 and < 25; Overweight BMI ≥ 25. 645 twins had both age 20 BMI data and age 48 health data. Three twins who reported diabetes at age 48 and seven twins with hypertension at age 48 did not have BMI data at age 20.

BMI and Health

Finally we examined the relationship between BMI status and two health outcomes associated with BMI. No twins reported being diabetic at age 20; blood pressure status at induction was unknown. BMI categories were collapsed to reflect normal (BMI > 16 and < 25) and overweight BMI (≥ 25) due to low frequencies of extremely low or high (obese) BMI at induction. Overweight BMI at age 20 was a significant predictor of adult onset diabetes; the association persisted after statistical adjustment for age, ethnicity, education, and twin pair clustering (adjusted OR = 4.62, 95% CI 1.91 to 11.18). However, age 20 BMI status (adjusted or unadjusted) did not predict whether a participant developed hypertension by age 48 (adjusted OR, 1.09, 95% CI .73 to 1.62). Of participants with normal BMI at age 20, only 2.7% reported diabetes at age 48. However, 11.2% of the overweight participants at age 20 were diabetic at age 48 (Table 2).

Overweight BMI status at age 48 was significantly associated with increased risk for diabetes (adjusted OR = 10.73, 95% CI 1.4 to 81.9) and hypertension (adjusted OR = 2.55, 95% CI 1.67 to 3.9). At age 48, only one person with diabetes was normal BMI, the remaining diabetic participants were all overweight. Hypertension was more prevalent among the overweight participants (42%) compared with 22.9% of normal BMI participants (see Table 3).

Discussion

The growing epidemic of excessive BMI and its concomitant health risks is highlighted in this 28-year longitudinal study. Average BMI at age 20 was 22.7 but at age 48 participants' average BMI was in the overweight range at 27.8. At age 20, only 1.7% of the participants were obese (BMI ≥ 30), while at age 48, 26.3% were obese. By comparison, in a twin sample of WWII veterans, BMI changed over an equivalent period from approximately 21.9 at induction, to 24.8 20 years later — in the normal range at both times. However, the phenotypic correlation of BMI over time in the WWII twin cohort (.54) was similar to that of this cohort (.52; Fabsitz et al., 1994; Feinleib et al., 1977; Stunkard et al., 1986). Differences between these two samples parallel the secular trends in BMI reported in non-twin samples (Gregg et al., 2005). Despite differences in analytic approach, genetic correlations were similar in the WWII twin sample and the Vietnam era twin cohort (.69 versus .60, respectively). Thus despite mean level changes in BMI, there is also stability in BMI, in that people tend to retain the same relative ranking within a sample.

In keeping with prior studies, additive genetic factors accounted for most of the proportion of variation in BMI at both times, though heritability was somewhat lower at midlife. Concomitantly, variation explained by nonshared environmental influences was higher at age 48 — perhaps reflecting greater differentiation between the twins in lifestyle factors such as activities (e.g., physical vs. sedentary lifestyle), diet, influences of partners, habits (e.g., smoking), or access to health care during adulthood. Genetic factors also accounted for the majority of the phenotypic stability in BMI (76%), consistent with other studies. Nevertheless, despite significant genetic overlap at the two times, because genetic factors were not perfectly correlated there is evidence of different genes affecting BMI at age 19, at age 48, or at both ages, leaving room for further exploration of the relative contributions of genetic and environmental influences on BMI variance and covariance over time. Unfortunately, with only two data points, we are limited to a correlated factors approach to these data, which makes it impossible to tell at which age the specific genetic influences are operating. Our study also cannot state with certainty whether the dramatic differences in *mean level* BMI are due to genetic or environmental factors. Consistent with recent, longitudinal, non-twin studies of BMI, our study finds a significant increase in rates of obesity in this sample of male twins over time. Given the similarity of our results regarding the magnitude of genetic and environmental influences on variation in BMI over time with previous twin studies, it seems unlikely that the new genes that come into play in midlife among twins from the Vietnam era cohort would be different from genes influencing BMI in the WWII cohort, which found more modest increases in BMI over time. Therefore, it seems likely

Table 3

Prevalence Rates — *N* Cases per BMI Group (per cent) — For Health Indicators at Age 48 and BMI Status at Age 48

	Body Mass Group at Age 48	
	Normal BMI (*N* = 166)	Overweight (*N* = 505)
Diabetes Age 48 (*N* = 32)	1 (0.6%)	31 (6.1%)
Hypertension Age 48 (*N* = 251)	38 (22.9%)	213 (42.2%)

Note: BMI = Body Mass Index. Prevalence rates = disease frequency in each BMI group. Normal BMI ≥ 18.5 and < 25; Overweight BMI ≥ 25. 671 twins had both health and BMI data at age 48.

that the differing trends with regard to increasing BMI with age in these two samples are due primarily to nonshared environmental factors.

At age 48, 251 participants (39.4%) had hypertension, and 32 (5.0%) reported having diabetes. The prevalence rate for hypertension is somewhat higher in this cohort than self-reported US national health statistics for this age group (29.8% in 45–64-year-olds), perhaps because our measure is based on a combination of objectively measured and self-reported hypertension, while the national statistics are based on self-report of having been told by a physician or health professional that a person had hypertension (NHANES III, 1999–2004). The self-reported rate for diabetes in American males age 45 to 64 is 10.3% as compared with 5.0% in this sample (NHANES III, 1999–2004). Several factors may account for the lower prevalence of diabetes in these participants. Our criteria for inclusion in the diabetes group required that participants self-report both that they were told by a physician they had diabetes, and that they were taking prescription medication for diabetes. NHANES statistics did not require that the person take medication for diabetes. In addition, our study participants are on the younger end of the NHANES age range and adult onset diabetes increases with age.

The relationship between early adult BMI and adult onset diabetes supports the growing alarm over the long-term public health implications of increasing adolescent/young adult body mass (Haffner, 2006; Lee et al., 2006). Recent reviews suggest that the steady rise in life expectancy over the past 2 centuries may come to an end, specifically due to the current trends in BMI (Olshansky et al., 2005; Thorpe, 2006). Rising overweight and obesity levels have obvious, substantial implications for health and health care costs (Elmer et al., 2004; Raebel et al., 2004). In this prospective study, being overweight, (not just obese), in early adult life created substantial risk for the development of diabetes in middle age.

Several aspects of the study limit the generalizability of the results. The sample comprises only male Caucasian twins from one cohort; prior research suggests some age, gender, ethnicity and cohort differences in heritability of BMI, as well as in the health consequences of BMI. In addition, genetic and environmental influences on individual differences in rates of BMI change over time cannot be accounted for when examining only two time points, as genetic versions of latent growth curve models require at least three data points. Finally, the categorical measures of diabetes and hypertension limit our ability to examine preclinical outcomes and risk factors. On the other hand, this sample represents a relatively healthy, low-risk sample of primarily middle-class men. The results indicate that overweight and obesity constitute a serious health problem for middle-class males, not just minorities or adults of lower socioeconomic status.

From a public health perspective, the genetics of BMI pose a conundrum. There are significant genetic influences on BMI, suggesting the potential for early identification of at-risk individuals, and for treatments aimed at biomedical interventions, yet gene-gene and gene-environment interactions need to be better delineated (Loos & Bouchard, 2003). Additionally, genetic factors uniquely associated with BMI still need to be identified, and further research is needed on the potential genetic overlap between BMI and chronic health problems, such as diabetes and hypertension. Recent research, for instance, identified a gene (FTO) that increases adult and child susceptibility to diabetes by increasing their risk for obesity (Frayling et al., 2007). Additionally, McCaffery and colleagues studied the clustering of risk factors associated with the metabolic syndrome. In young adult twins, covariation of systolic and diastolic blood pressure (BP), BMI, total cholesterol, and triglycerides was partially attributable to a single common genetic factor, while the covariation of systolic BP, BMI, and triglycerides was also, in part, attributable to a common nonshared environmental factor (McCaffery et al., 1999). A meaningful proportion of the variation in BMI over time is also accounted for by unique environment factors, leaving open multiple avenues for behavioral interventions and interventions targeted at modifying obesogenic environments.

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