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Genetic and environmental contributions to body mass index: comparative analysis of monozygotic twins, dizygotic twins and same-age unrelated siblings

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Abstract

Background—Earlier studies have established that a substantial percentage of variance in obesity-related phenotypes is explained by genetic components. However, only one study has used both virtual twins (VTs) and biological twins and was able to simultaneously estimate additive genetic, non-additive genetic, shared environmental and unshared environmental components in body mass index (BMI). Our current goal was to re-estimate four components of variance in BMI, applying a more rigorous model to biological and virtual multiples with additional data. Virtual multiples share the same family environment, offering unique opportunities to estimate common environmental influence on phenotypes that cannot be separated from the non-additive genetic component using only biological multiples.

Methods—Data included 929 individuals from 164 monozygotic twin pairs, 156 dizygotic twin pairs, five triplet sets, one quadruplet set, 128 VT pairs, two virtual triplet sets and two virtual quadruplet sets. Virtual multiples consist of one biological child (or twins or triplets) plus one same-aged adoptee who are all raised together since infancy. We estimated the additive genetic, non-additive genetic, shared environmental and unshared random components in BMI using a linear mixed model. The analysis was adjusted for age, age^2, age^3, height, height^2, height^3, gender and race.

Results—Both non-additive genetic and common environmental contributions were significant in our model (*P*-values < 0.0001). No significant additive genetic contribution was found. In all, 63.6% (95% confidence interval (CI) 51.8–75.3%) of the total variance of BMI was explained by a non-additive genetic component, 25.7% (95% CI 13.8–37.5%) by a common environmental component and the remaining 10.7% by an unshared component.

Conclusion—Our results suggest that genetic components play an essential role in BMI and that common environmental factors such as diet or exercise also affect BMI. This conclusion is consistent with our earlier study using a smaller sample and shows the utility of virtual multiples for separating non-additive genetic variance from common environmental variance.

Keywords

twins; virtual twins; body mass index

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Introduction

Genetic influence on body mass index (BMI) has been documented by numerous behavioral genetic studies, yielding heritability estimates of 25–75%.[1] In contrast, the contribution to BMI from shared environmental factors has been less certain. This is because non-additive genetic effects and common environmental effects are confounded in ordinary twin designs, such that a large non-additive genetic effect will obscure a more modest common environmental effect. It is, therefore, likely that common environmental effects have been underestimated in the literature due, in part, to the lack of genetically and environmentally informative kinships.

Segal and Allison[2] attempted to rectify this situation with a combined twin–virtual twin (VT) design. VTs are same-age unrelated siblings, reared together since infancy. They may be composed of two adoptees, or one adoptee and a biological child.[3–5] VTs replicate the twin situation, but without the genetic link, providing a pure estimate of shared environmental influence. These pairs improve upon ordinary adoption designs, given that they are matched in age, placement history and other life history measures. The analysis by Segal and Allison[2] yielded evidence of non-additive genetic effects (61%), shared environmental effects (25%) and non-shared environmental effects (14%) on BMI.

A further limitation of studies using higher order multiples (that is, triplets and quadruplets) is their restriction to cross-sectional and cohort studies.[6] Few genetic studies incorporate such multiples, which also require additional zygosity information within the multiple sets. Furthermore, triplet and quadruplet sets are often reorganized as several separate twin pairs and analyzed accordingly, a practice that could violate the independence assumption across twin sets; this would result in biased estimates of genetic and environmental effects. Advanced modeling techniques are needed to incorporate the within-group correlation to estimate genetic components and environmental effects for quantitative traits. An opportunity to revisit these issues became available with much larger twin and VT samples.

Methods

Sample description

Participants were drawn from five studies concerned with behavioral similarity, behavioral adjustment and social relatedness in twins, siblings and best friends. TAPS (Twins, Adoptees, Peers and Siblings), a joint collaboration between California State University, Fullerton, and the University of San Francisco,[4,5] provided pairs in all participant categories (MZ: $n = 54$; DZSS: $n = 51$; DZOS: $n = 35$; VT: $n = 1$). Twins were also identified in studies conducted at the University of Chicago[7,8] (MZ: $n = 70$; DZSS: $n = 35$), the University of Minnesota[9] (MZ: $n = 44$; DZSS: $n = 46$) and CSU Fullerton[10] (DZOS: $n = 20$). VT pairs came mostly from the Fullerton Virtual Twin Study at CSU Fullerton[2,3,11–13] (VT: $n = 138$). Members of several twin and VT triplet and quadruplet sets were organized into pairs for purposes of the sample description, although each participant was entered only once in the mixed model analyses.

Twins in the different studies were identified primarily through mothers of twin clubs, although many sets were found through letters to schools and organizations, flyers posted in local communities, personal referrals and newspaper advertizing. VTs were additionally identified through adoption organizations and adoption websites. These pairs resided in many locations across the United States and Canada. The mean age difference between VT co-twins was 3.23 months (s.d. = 2.77), range: 0–9.23, and the mean age at adoption for the

223 adoptees was 1.73 months (s.d. = 2.91), range: 0–12.43. Ninety-one pairs included two adoptees, and 48 pairs included an adoptee and a biological child.

Zygosity determination

The zygosity of the same-sex twin pairs in TAPS was established by comparative examination of 13 short tandem repeat DNA markers. The zygosity of approximately half the pairs in the University of Chicago and University of Minnesota studies was established by extensive serological assessment. The zygosity of the remaining twins in those two studies was assigned by scores on a standard physical resemblance questionnaire developed by Nichols and Bilbro;[14] this form shows 93% agreement with the results from blood typing. Male–female twin pairs in TAPS and at CSU Fullerton were classified as DZ because of their sex difference.

Data collection

Weight and height for the TAPS and University of Minnesota participants were gathered by investigators as part of a standard assessment battery. Each team of examiners used the same scale and measuring stick that they brought to the twins' homes or used in the laboratory. These data were provided by University of Chicago study parents who weighed and measured the twins during home visits or shortly thereafter. DZ opposite-sex twins in the CSUF study were weighed and measured by investigators during visits to the Twin Studies Center laboratory. Parents of VTs in the Fullerton Virtual Twin Study weighed and measured their children at home or provided their children's weight and height from a recent medical visit. They entered these data in research packets that they received by mail; adult VT pairs also provided this information in their packets. Twins in 14 pairs were deleted due to missing weight data.

The twins' ages were recorded as their age at the time of assessment. The only exceptions were related to the VTs whose parents forwarded their research packets before or after the day that their children were assessed. In these cases, age was based on the day that the parent completed the packet or provided the data to the investigators. The MZ and DZ twin pairs did not differ in age (9.53 years, s.d. = 2.56, n = 166 and 9.40 years, s.d. = 2.04, n = 173, respectively), although both groups were significantly older than the VT pairs (8.01 years, s.d. = 8.29, n = 138). The ethnicity of the child participants was provided by their parents, whereas adult participants provided this information by self-report. The majority of participants were Caucasian (76.53%), with the remainder classified as mixed (9.90%), Hispanic (4.20%), African-American (3.23%), Asian (3.12%), South American Indian (1.61%), North American Indian/Alaskan Native (0.65%) and others (0.75%). Descriptive characteristics for the final sample are provided in Table 1.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Approval by the appropriate Ethical Committees at California State University, Fullerton, the University of San Francisco, the University of Minnesota and the University of Chicago was obtained.

Statistical analysis

Linear mixed-effects regression variance components models with maximum likelihood estimation were used to estimate the genetic and environmental contributions to BMI, adjusting for the covariates of age, gender and race.[15] In this model, BMI is assumed to follow a normal distribution with the mean determined by the covariates, and the variance partitioned into an additive genetic component, a non-additive genetic component, a shared non-genetic component and a random component. Specifically,

$$Y_{ij}=X_{ij}\cdot\beta+a_{ij}+d_{ij}+c_i+\varepsilon_{ij} \quad (1)$$

where Y_{ij} is the BMI for the *j*th subject in the *i*th set of multiples. In addition, X_{ij} is a vector of covariates including age, age^2, age^3, height, height^2, height^3, gender and race for the *j*th subject in the *i*th set of multiples, β measures the covariate effects (including an intercept), and a_{ij}, d_{ij}, c_j and ε_{ij} are, respectively, the additive genetic, non-additive genetic, common environmental and residual environmental random effects on the *j*th subject in the *i*th multiple set. If two sibs *j* and *k* (either twins or a couple within a triplet set or a quad set) are MZ, that is, genetically identical, $a_{ij} = a_{ik}$ and $d_{ij} = d_{ik}$. It was assumed that *a*, *d*, *c* and ε (the subscripts are sometimes suppressed for convenience) are independently normally distributed with mean 0 and variance σ_a^2, σ_d^2, σ_c^2 and σ_e^2, respectively. If two sibs *j* and *k* are MZ, the covariances of *a* and *d* between them are $\mathrm{cov}(a_{ij}, a_{ik})=\sigma_a^2$ and $\mathrm{cov}(d_{ij}, d_{ik})=\sigma_d^2$, respectively. If two sibs *j* and *k* are DZ, the covariances of *a* and *d* between them are $\mathrm{cov}(a_{ij}, a_{ik})=\sigma_a^2/2$ and $\mathrm{cov}(d_{ij}, d_{ik})=\sigma_d^2/4$, respectively.[15] The model was fit using SAS PROC MIXED. The heritability of BMI can then be estimated using the ratio of the estimated genetic variance and the total variance of BMI.

The mixed model for weight was adjusted for age, age^2, age^3, gender, race, height, height^2 and height^3. The 95% confidence intervals were constructed using SAS PROC NLMIXED, which approximates the standard errors of the variance components by a first-order Taylor series of non-linear functions of the parameters.[16]

Results

Descriptive statistics

Means, standard deviations and intraclass correlations for body weight, height and BMI are presented for the three twin groups in Tables 2–4. MZ and DZ twins did not differ in body weight or height, but both groups were significantly taller and heavier than the VTs. Twin group differences in BMI were not found.

To calculate intraclass correlations, the data for the full sample were corrected for the effects of age (up to the third degree polynomial, sex and the interaction of sex with each polynomial of age) and were then standardized (mean = 0 and s.d. = 1). The regression procedures for age and sex corrections are well documented in the literature.[17] The MZ intraclass correlations for all three measures significantly exceeded both the DZ and VT correlations. Similarly, the DZ correlations significantly exceeded the VT correlations. These results are generally mirrored by the relative magnitudes of the within-pair differences.

Variance decomposition

The estimates of σ_a^2, σ_d^2, σ_c^2 and σ_e^2 are 0, 4.27, 1.72 and 0.72 and the latter three are significant (*P*-values < 0.0001), that is, both dominant genetic and common environmental contributions are significant. The additive genetic contribution was not significant and, thus, was dropped from the model when estimating the confidence intervals for the components. The heritability of BMI was 63.56% (95% confidence interval (CI) 51.79–75.33%) and the genetic component was essentially non-additive. A common environmental component explained 25.66% (95% CI 13.79–37.54%) of the total variance of BMI and a shared component explained the remaining 10.78%.

The model using body weight as the response (*Y*) adjusted for the above covariates resulted in variance components within 2% of those in BMI. This finding is consistent with the definition of BMI and confirms our model's robustness.

Our findings suggest that non-additive genetic components play an essential role in relative body weight and that common environmental factors, such as diet or exercise, also affect relative weight significantly.

Fixed effect estimate

All important covariates were included in the mixed effects model; estimated covariate effects for BMI are shown in Table 5. All covariates, but race ('other' race as the reference group), were significant.

Discussion

This study underlines the utility of using both biological multiples and virtual multiples in a combined analysis of BMI. Most earlier twin studies of BMI have underestimated the common environmental components because they cannot distinguish the non-additive genetic component from shared environmental influences. The only other study[2] that includes both twins and VTs yielded findings similar to the present ones. Most importantly, this study used a more rigorous model that incorporates genetic correlations within multiples more efficiently than models based on pairs only.

Dominance effects are well-known sources for non-additive genetic components.[18,19] Epigenetic effects or maternal effects could lead to unbalanced expression of genes from parental alleles and, thus, could show up as non-additive genetic effects. Studies have found a close relationship between dominance and imprinting.[20,21] Gene-by-gene interactions may also result in non-additive genetic effect on traits.

Study limitations

Our statistical model relies on various assumptions whose validity is hard to check using the current sample. For example, we assumed an equal common environmental effect for VTs. More specifically, VTs do not share the same intrauterine environment or the same social environment before adoption, both of which could affect birth weight through nutritional availability. Embryo transfer studies in humans and animals have shown that the maternal environment in which the fetus develops influences birth weight to a greater extent than the genome.[22,23] Additional genomic information can be used for genome-wide scans to locate genes or isolate genes associated with relative weight, which is beyond the scope of this study. Heritability can also be estimated more accurately using actual gene sharing for sibling pairs, rather than average sharing, and we recommend such studies in the future.[24]

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Table 1

Descriptive characteristics of twins and virtual twins

Zygosity *n* (pairs/individual)	Mean age (year)[a] (s.d.)	Range	MM	FF	OS
MZ[b] 166/333	9.53 (2.56)	5.11–23.25	71	95	—
DZ[c] 173/326	9.40 (2.04)	6.14–16.74	69	54	50
VT[d] 138/270	8.01 (8.29)	3.93–55.51	39	30	69
FULL 477/929	9.04 (4.92)	3.93–55.51	179	179	119

FF = female pairs; MM = male pairs; OS = opposite-sex pairs.

[a] Ages are reported as individual data ($n = 929$).

[b,d] $F = 38.30$, $P < 0.001$, $t(310.63) = 2.89$, $P < 0.01$.

[c,d] $F = 48.14$, $P < 0.001$, $t(296.05) = 2.69$, $P < 0.01$.

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Table 2

Means, standard deviations, intraclass correlations and 95% confidence intervals for twins' and virtual twins' body weight

Zygosity *n* (pairs/individual)	Weight in lb (s.d.), range[a]	r_i	95% CI	Within-pair difference
MZ	70.39 (25.51)	0.89***	0.85–0.92	4.71 (5.57)
166/333	33.00–171.00	00.00–31.00		
DZ	71.23 (24.31)	0.45***	0.32–0.56	11.89 (13.59)
173/326	40.00–171.50	00.00–99.50		
VT	56.37 (35.55)	0.24**	0.08–0.39	9.47 (14.21)
138/270	28.00–250.00	00.00–108.00		

Abbreviations: CI = confidence interval, r_i = intraclass correlation.

** $P < 0.01$;

*** $P < 0.001$.

MZrr$_i$>DZr_i, $P < 0.001$; MZr_i>VTr$_i$, $P < 0.001$; DZr_i>VTr$_i$, $P < 0.05$.

Intraclass correlations derive from analysis of variance mean squares between (MSB) and within (MSW): (MSB−MSW)/(MSB+MSW).

[a] Weight is reported as individual data.

MZ>VT: $t(473.55) = 5.44$, $P < 0.001$. DZ>VT: $t(460.52) = 5.83$, $P < 0.001$.

Table 3

Means, standard deviations, intraclass correlations and 95% confidence intervals for twins' and virtual twins' height

Zygosity *n* (pairs/individual)	Height in inches (s.d.) Range[a]	r_i	95% CI	Within-pair difference
MZ	53.17 (5.63)	0.94***	0.92–0.96	0.68 (0.67)
166/333	42.00–70.75			0.00–5.00
DZ	53.64 (5.13)	0.55***	0.44–0.65	1.96 (1.63)
172/324	42.00–68.25			(0.00–9.75)
VT	46.51 (8.21)	0.27***	0.11–0.42	2.24 (2.19)
137/268	36.00–74.25			(0.00–11.00)

[a] Height is reported as individual data.

** $P < 0.01$;

*** $P < 0.001$.

MZrr$_i$>DZr_i, $P < 0.001$; MZr_i >VTr_i, $P < 0.001$; DZr_i >VTr_i, $P < 0.01$.

MZ>VT: $t(455.03) = 11.31$, $P < 0.001$. DZ>VT: $t(430.11) = 12.35$, $P < 0.001$.

Table 4

Means, standard deviations, intraclass correlations and 95% confidence intervals for twins' and virtual twins' BMI

Zygosity *n* (pairs/individual)	BMI (s.d.) Range[a]	r_i	95% CI	Within-pair difference
MZ	16.91 (2.94)	0.87***	0.83–0.90	0.87 (0.99)
166/333	12.41–28.29			0.00–6.01
DZ	17.02 (3.24)	0.48***	0.36–0.59	2.18 (2.31)
172/324	11.33–31.88			0.00–12.98
VT	16.99 (3.44)	0.25**	0.09–0.40	1.89 (2.50)
137/268	12.96–44.29			0.00–15.84

Abbreviations: BMI, body mass index; CI, confidence interval.

** $P < 0.01$;

*** $P < 0.001$.

MZrr$_i$>DZr_i, $P < 0.001$; MZr_i >VTr_i, $P < 0.001$; DZr_i >VTr_i, $P < 0.01$.

[a] BMI is reported as individual data.

Table 5

Estimated covariates effects for BMI

Variables	Estimate	Standard error (s.e.)	*P*-value
Height	−6.617	0.093	<0.0001
Height^2	0.125	0.004	<0.0001
Height^3	−0.0008	0.00004	<0.0001
Age	−0.589	0.217	0.0068
Age^2	0.035	0.010	0.0003
Age^3	−0.0004	0.0001	0.0004
Sex	−0.226	0.187	0.2294
Race			
African-American	1.341	0.522	0.0106
American Indian/Alaska Native	2.170	0.043	<0.0001
Asian	−0.520	0.496	0.2946
White	−0.430	0.232	0.0640
Hispanic	1.061	0.439	0.0160
South American Indian	1.220	0.612	0.0468
Mixed	0.179	0.323	0.5796

Abbreviation: BMI, body mass index.