

Childhood Obesity: Genetic and Environmental Overlap With Normal-range BMI

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Objective: To understand the overlap between the etiology of obesity and normal variation in BMI in children.

Methods and Procedures: Height and weight data were available from a large UK representative sample of twins: 2,342 same-sex pairs at 7 years and 3,526 same-sex pairs at 10 years. The twin method and model-fitting techniques were used to estimate genetic and environmental contributions to BMI. DeFries–Fulker (DF) extremes analysis was used to investigate genetic and environmental influences on the mean difference between obese and normal-weight children. Obesity was classified using the International Obesity Task Force (IOTF) criteria.

Results: At both ages, BMI and obesity were highly heritable (0.60–0.74) and only modestly influenced by shared environmental factors (0.12–0.22). Extremes analyses indicated that genetic and environmental influences on obesity are quantitatively and qualitatively similar to those operating across the range of BMI.

Discussion: Obesity is the extreme of the same genetic and environmental factors responsible for variation throughout the distribution of BMI. This finding implies that genes that influence obesity will also be associated with BMI in the normal range, and similar environmental influences will affect BMI in the clinical and normal range. Knowing that obesity is influenced by the same genetic and environmental factors that affect weight at all levels has implications for investigating the mechanisms for weight gain and developing interventions for weight control.

Obesity (2008) **16**, 1585–1590. doi:10.1038/oby.2008.240

INTRODUCTION

Quantitative genetic research consistently points to substantial genetic influence on individual differences in BMI, although the extent of the genetic effect size (heritability) has varied between studies. Heritability estimates of BMI from twin studies range from 50 to 90% (1).

It cannot be assumed that obesity is affected by the same genetic and environmental factors responsible for variation in the normal range of BMI; indeed, the search for “obesity genes” can imply that there are different genetic factors. A recent review has suggested that there will be little overlap between genes for normal weight and those for obesity (2). There have been two previous twin studies of obese individuals, but neither compared the etiology of obesity to normal weight (3,4). A previous report from the present sample at 4 years of age suggested that high body weight was the quantitative extreme of the same genetic and environmental influences that operate throughout the distribution of weight (5), but the analysis did not use recognized criteria to define the obese probands. This report follows up this finding by considering the etiology of BMI and obesity at 7 and 10 years in the same large sample of twins and using an internationally recognized criterion (from the International Obesity Task Force; IOTF) to define obesity.

DeFries–Fulker (DF) extremes analysis (6) at each age was applied to investigate the extent to which obesity is etiologically distinct from normally distributed BMI. On the basis of previous research, we expected to find that BMI is highly heritable in childhood and that shared family environment would make a minor contribution to obesity and normal variation in adiposity (7). We expected to find some genetic overlap between the etiology of BMI and obesity but the extent of genetic overlap is not known.

METHODS AND PROCEDURES

Sample

The sampling frame for this study was the Twins’ Early Development Study (TEDS), a study of twins born in England and Wales in 1994, 1995, and 1996 (8). The TEDS sample has been shown to be reasonably representative of the population (9); TEDS is described in more detail elsewhere (8,9). TEDS research was approved by the Institute of Psychiatry Ethics Committee, and all participants gave informed consent.

At 7 years, 8,163 families (56%) consented to take part, of whom, 7,896 families returned questionnaires. At 10 years, of the 12,212 families to whom the eating behavior questionnaire was sent, 8,978 were “active participants” in TEDS at the time of data collection. A total of 5,543 of them returned completed questionnaires (61.7%). Of the remaining 3,234 families who were not “currently active”, a further 359 returned completed

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Received 1 February 2007; accepted 1 October 2007; published online 17 April 2008. doi:10.1038/oby.2008.240

questionnaires resulting in a total sample of 5,906 families (representing 48.3% of the entire original sample). Not all families provided both height and weight measurements for their children. We had complete BMI data for 6,641 individuals at 7 years and 10,856 individuals at 10 years. We excluded from the analyses families in which at least one member of the twin pair had a specific medical syndrome or was an extreme outlier for perinatal problems such as extreme low birth weight. Medical syndromes included genetic and chromosomal disorders (e.g., Down syndrome), brain disorders, profound blindness or deafness, and global developmental delay. Criteria for raw data cleaning were based on the ranges of measured heights and weights from the Health Survey for England 2003 (see <http://www.archive2.official-documents.co.uk/document/deps/doh/survey03/hse03.htm> for more details). Heights <1.10 m and weights <13 kg and >84 kg were excluded. When BMI was calculated from the cleaned data, we also excluded individuals with a BMI <12. These analyses were limited to same-sex twin pairs, because the DF extremes analysis technique allows for same-sex pairs only. The final individual differences analysis included 2,342 twin pairs at 7 years (1,346 monozygotic (MZ) pairs, 996 dizygotic (DZ) same-sex pairs) and 3,526 twin pairs at 10 years (1,857 MZ pairs, 1,669 DZ same-sex pairs). This final sample was reasonably representative of the general UK population in terms of demographic variables such as socioeconomic status and parental education. Further information about the representativeness of TEDS can be found elsewhere (9). The mean age of the twins when questionnaires were returned from parents at the two assessments were 7.05 (s.d. = 0.25) and 9.91 (s.d. = 0.87). Zygosity was assessed through a parent questionnaire of physical similarity, which has been shown to be >95% accurate when compared to DNA testing (10). Where zygosity was unclear from this questionnaire, DNA testing was conducted.

Proband

For the extremes analysis, we selected twin pairs where one or both members were classified as obese based on IOTF categories (described below) (11). The obese group at 7 years included 106 probands in 80 families (36 MZ and 44 DZ pairs). The obese group at 10 years included 194 probands in 154 families (58 MZ and 96 DZ pairs).

Measures

Child height and weight data were collected from the parents when their twins were 7 and 10 years of age. Parents were provided with a tape measure to aid the measurement of height. They were asked to indicate whether they had weighed the children themselves and when they were weighed. Ninety-four percent of parents reported that they had weighed the twins themselves. BMI was calculated from height and weight ($BMI = \text{weight (kg)} / (\text{height (m)}^2)$). BMI z-scores take account of the child's age and sex. They are based on 1990 UK growth reference curves (12) and were calculated using the program *lmsGrowth* (available from <http://homepage.mac.com/tjcole>). Children were categorized as normal weight, overweight, or obese using IOTF criteria (11), which are based on age- and sex-specific cutoff points linked to growth curves, and correspond to BMI criteria for normal weight, overweight, and obesity in adults (11).

Analyses

One of the major methods used in quantitative genetics to estimate genetic and environmental influences is the twin method (13–15). This design allows researchers to investigate the genetic and environmental influences on individual differences (variance) in observed traits (called phenotypes). Twinning provides naturally occurring quasiexperimental comparisons. The twin method requires both identical twins (MZ) and nonidentical twins (DZ). MZ twins are 100% genetically similar, whereas DZ twins are on average only 50% similar for segregating genes. This contrast in genetic similarity implies that to the extent that a trait is influenced by genetics the within-pair resemblance for that trait should be greater in MZ twins than in DZ twins. By comparing the twin intraclass correlations, it is possible to estimate genetic effects, shared

environmental effects (i.e., environmental effects that make children in the same family more similar) and nonshared environmental effects (i.e., environmental effects that make children growing up in the same family different). These three effects are commonly known as A, C, and E, respectively. Shared environmental influences may be factors such as family diet and exercise patterns, but only if these influences act in such a way as to make the twins more similar to one another. Nonshared environmental influences are those that make twins in a pair less similar, for example an accident experienced by only one twin in the pair. A more elegant way of estimating the A, additive genetic; C, shared environment; E, nonshared environment parameters is maximum likelihood model-fitting analysis (14), which makes assumptions explicit, tests the fit of the entire model to the data, tests the relative fit of alternative models, and provides confidence intervals for the parameter estimates. Discussions of the use of maximum likelihood model-fitting analyses can be found elsewhere (14–16). We carried out model-fitting analyses for BMI z-scores at each age for the whole sample. Mx software for structural equation modeling was used for standard analyses using raw data (16).

Extremes analysis. A major goal was to examine the etiology of obesity specifically. Twin pairs where at least one member of the pair was classified as obese were selected for the extremes analysis at each age. Probandwise concordances (the ratio of the number of probands in concordant pairs to the total number of probands) were calculated to quantify the risk that a co-twin of a proband is affected. Greater MZ than DZ concordances suggest genetic influence, but unlike twin correlations, twin concordances cannot be used to estimate genetic and environmental parameters because they do not themselves include information about population incidence.

DF extremes analysis assesses genetic links between the extreme and the normal range by bringing together the dichotomous classification of obesity and the quantitative trait of BMI. Rather than assessing twin similarity in terms of individual differences on a quantitative trait of BMI or concordance for a diagnostic cutoff, DF extremes analysis assesses twin similarity as the extent to which the mean standardized quantitative trait score of co-twins of the selected extreme probands is above the population mean and approaches the mean standardized score of those probands (17). This measure of twin similarity is called a group twin correlation (or transformed co-twin mean) in DF extremes analysis because it focuses on the mean quantitative trait score of co-twins rather than individual differences. Genetic influence is implied if group twin correlations are greater for MZ than for DZ twins, that is, if the mean standardized score of the co-twins is higher for MZ pairs than for DZ pairs (Figure 1). Doubling the difference between MZ and DZ group twin correlations estimates the genetic contribution to the average phenotypic difference between the probands and the population. The ratio between this genetic estimate and the phenotypic difference between the probands and the population is called group heritability. It should

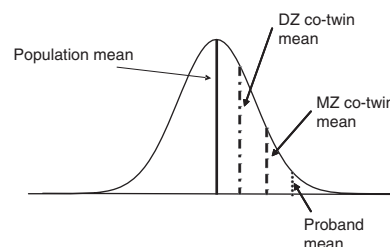


Figure 1 DeFries–Fulker extremes analysis assesses twin similarity as the extent to which the mean standardized quantitative trait score of co-twins is similar to the mean standardized score of selected extreme or diagnosed probands. This measure of twin similarity is called a group twin correlation in DeFries–Fulker extremes analysis because it focuses on the mean quantitative trait score of co-twins rather than individual differences. DZ, dizygotic; MZ, monozygotic.

be noted that group heritability does not refer to individual differences among the probands—the question is not why one proband is slightly more obese than another but rather why the probands as a group have higher BMI than the rest of the population.

Although DF extremes group heritability can be estimated by doubling the difference in MZ and DZ group twin correlations (18), DF extremes analysis is more properly conducted using a regression model (6). The DF extremes model fits standardized scores for MZ and DZ twins to the regression equation:

$$C(X) = B_1P(X) + B_2R + A$$

where the co-twins' BMI scores ($C(X)$) are predicted from the probands' BMI scores ($P(X)$) and the coefficient of relatedness (R), which is 1.0 for MZ (genetically identical) and 0.5 for DZ twins (who are on average 50% similar genetically), and A is the regression constant. B_1 is the partial regression of the co-twin score on the proband, an index of average MZ and DZ twin resemblance independent of B_2 . The focus of DF extremes analysis is on B_2 . B_2 is the partial regression of the co-twin score on R independent of B_1 . It is equivalent to twice the difference between the means for MZ and DZ co-twins adjusted for differences between MZ and DZ probands. In other words, B_2 is the genetic contribution to the phenotypic mean difference between the probands and the population. Group heritability is estimated by dividing B_2 by the difference between the means for probands and the population.

Finding group heritability implies that both obesity and normal BMI are heritable, and that there are genetic links between obesity and normal variation in BMI. That is, group heritability itself, not the comparison between group heritability and the other estimates of heritability, indicates genetic links between obesity and normal BMI. If a measure of extremes (or a diagnosis) were not linked genetically to a quantitative trait, group heritability would be zero. This situation could occur if a severe rare form of obesity were due to a single-gene disorder that contributes little to normal variation in BMI. However, most researchers now believe that disorders such as common obesity are caused by common genetic variants—the common disease/common variant hypothesis (19)—rather than a concatenation of rare single-gene disorders. To the extent that the same genes contribute to obesity and normal variation in BMI, group heritability will be observed, although the magnitude of group heritability depends on the individual heritability for normal variation and the heritability of obesity gleaned from concordances for obesity.

RESULTS

At 7 years, mean BMI was 15.69 (s.d. = 1.97) and at 10 years 17.14 (s.d. = 2.90). Minimum and maximum scores for BMI were 12 and 37 at 7 years, and 12 and 46 at 10 years. Using IOTF categories, 9 and 11% of the children were overweight at 7 and 10 years, respectively, and an additional 2.3 and 2.8% were obese at 7 and 10 years (see Table 1).

Table 1 Means (s.d.) for height, weight, BMI, and BMI z-scores for the full sample and the obese probands at 7 and 10 years

	7 Year		10 Year	
	Full sample (n = 4,684)	Obese probands (n = 106)	Full sample (n = 7,052)	Obese probands (n = 194)
Height (m)	1.23 (0.06)	1.25 (0.06)	1.39 (0.08)	1.42 (0.09)
Weight (kg)	23.43 (4.11)	35.47 (4.22)	33.42 (7.88)	53.82 (9.15)
BMI	15.69 (1.97)	22.49 (1.87)	17.14 (2.90)	26.88 (4.22)
BMI z-score	-0.14 (1.16)	2.71 (0.47)	0.00 (1.17)	2.78 (0.50)

N value is given as number of individuals.

Analysis of individual differences in the normal distribution. Across the whole sample, MZ correlations exceeded those of the DZ twins at both ages (see Table 2), suggesting genetic influence. Doubling the difference between the MZ and the DZ correlations to estimate heritability indicates substantial genetic influence on BMI at age 7 (0.60) and age 10 (0.72). Estimates of the shared environment—subtracting the heritability estimates from the MZ twin correlation—were consistently modest for BMI (average 0.18). Model-fitting results confirmed these findings with heritability estimated as 0.60 and 0.74 at 7 and 10 years, and shared environment as 0.22 and 0.12, respectively (Table 2). The model fitted the data well compared to a saturated model that does not partition the variance into A , C , and E , and explains the data perfectly.

Extremes analysis. Probandwise concordances are shown in Table 3. They indicate strong genetic influence because

Table 2 Individual differences results for BMI z-scores at 7 and 10 years of age; A, C, and E

	Intraclass correlations	A	C	E
7-Year BMI	MZ = 0.81 (n = 1,346) DZ = 0.51 (n = 996)	0.60	0.21	0.19
10-Year BMI	MZ = 0.86 (n = 1,857) DZ = 0.50 (n = 1,669)	0.72	0.14	0.14
Model-fitting estimates (95% confidence intervals)				
7-Year BMI		0.60 (0.52–0.69)	0.22 (0.13–0.30)	0.18 (0.16–0.19)
10-Year BMI		0.74 (0.68–0.81)	0.12 (0.06–0.19)	0.13 (0.12–0.14)

Estimates from intraclass twin correlations and from structural equation maximum likelihood model-fitting analyses.

A, additive genetic; C, shared environment; DZ, dizygotic twins; E, nonshared environment; MZ, monozygotic twins.

N value is number of twin pairs.

Table 3 Twin results for obesity: MZ and DZ probandwise concordances, twin group correlations and results of DF extremes analysis at 7 and 10 years

	Probandwise concordance		Twin group correlation		DF estimates	
	MZ	DZ	MZ	DZ	h ² g (SE)	c ² g (SE)
7-Year BMI (106 Probands)	0.67	0.31	0.89	0.55	0.68 (0.16)	0.21 (0.14)
10-Year BMI (194 Probands)	0.64	0.24	0.90	0.55	0.70 (0.12)	0.20 (0.10)

For the extremes analysis, we selected twin pairs where one or both members were classified as obese based on the IOTF categories. The obese group at 7 years included 106 probands in 80 families (36 MZ and 44 DZ pairs). The obese group at 10 years included 194 probands in 154 families (58 MZ and 96 DZ pairs).

h²g (group heritability) indicates genetic influence on the mean difference between the proband group and the population. Similarly, c²g indicates group-shared environmental influence. See text for explanation of probandwise concordance and twin group correlation.

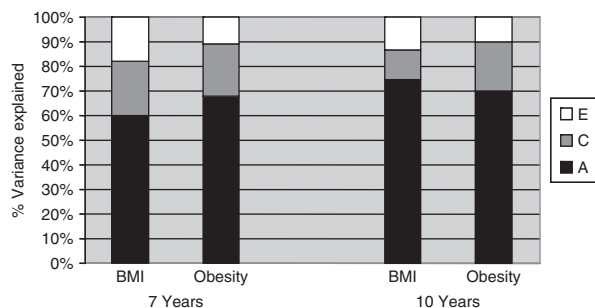


Figure 2 Results are highly similar for individual differences and DeFries–Fulker extremes results for BMI and obesity at 7 years and 10 years. Note: A, additive genetic; C, shared environment; E, nonshared environment.

concordance rates for obesity were higher for MZ twins than those for DZ twins. Average MZ and DZ concordances for obesity across the two ages were 0.66 and 0.28, respectively (Table 3).

Table 3 also presents the results from the DF extremes analysis, which gives estimates of group heritability and group environmental influences. Group heritability of obesity was substantial: 0.68 and 0.70 at 7 and 10 years, respectively. In contrast, group-shared environmental influences were modest at 7 and 10 years (0.21 and 0.20). Group nonshared environmental influences accounted for the remaining variance, and included measurement error. The results of the DF extremes analyses were very similar to the results of the individual differences analyses for the full sample, as shown in Figure 2.

DISCUSSION

The abnormal is normal

We found similar estimates for individual differences heritability of BMI (0.60 and 0.74 at 7 and 10 years, respectively) and group heritability of obesity (0.68 and 0.70). The DF extremes analysis directly addresses the issue of qualitative similarity in etiology.

Finding group heritability (genetic influence on the mean difference in BMI between probands and the population) implies genetic links between obesity and BMI, and finding group-shared environment implies environmental links. Therefore, DF extremes analysis itself, not the comparison between the results for DF extremes analysis and analysis of individual differences, speaks to whether there are qualitative differences in the genetic and environmental influences. Group heritability and group-shared environment will be observed to the extent that there are links between obesity and BMI (17); if obesity were under the control of different determinants than BMI, the co-twins' mean would regress back to the population mean.

Finding genetic overlap between obesity and normal BMI variation supports the quantitative trait locus model of molecular genetics (20). The basis of the quantitative trait locus model is that many genes of small effect are responsible for the heritability of common disorders and continuous (quantitative) traits; implying that common disorders are the quantitative extreme of the same genetic effects that operate throughout

the distribution. When genes are found that contribute to obesity, the same genes would be expected to contribute to normal variation in BMI. Of course, there are rare, monogenic forms of obesity (2), but the genetic effects found here are not likely to be the result of such severe and rare disorders because we excluded from the analysis all individuals with serious medical conditions.

Thus, we conclude that these results support the hypothesis that, for obesity, the abnormal is normal both quantitatively and qualitatively, and for genetic and environmental influences.

Environmental influences

Just as important as the genetic results is the finding that for both BMI and obesity there is relatively little shared environmental influence (average shared environment = 0.17; average group-shared environment = 0.21), despite the twins living in the same home and going to the same school. Familial influence is largely genetic in origin and this is confirmed by studies of MZ twins reared apart (21). Estimates for shared environment appear to decrease with age from 0.22 at age 7 to 0.12 at age 10, consistent with higher shared environment estimates at birth of 0.40 (22). The finding of low shared environment does not mean that the family environment is unimportant for the regulation of BMI. However, it does mean that if these factors are influencing BMI then they are explained (in the twin-model) instead as nonshared environmental factors (environments that make twins in a pair different) or as genetic influences. It is possible that family environmental factors such as eating behavior and attitudes toward exercise are themselves under significant genetic influence (23).

Most studies of BMI in adulthood show that environmental influences are of the nonshared rather than the shared variety (7,24). These analyses have shown that in middle childhood, shared and nonshared environmental influences are equal in magnitude, together accounting for, on average 33% of the variance in BMI. Therefore, total environmental influence (shared and nonshared) accounts for a significant proportion of the variance (average 33%), and cannot be disregarded. Future research should aim to identify specific environments that influence adiposity. It is also possible that environments interact with genetic risk so that the genetic influence is stronger (or weaker) in higher-risk environments. It is important that future work considers both genetic and environmental influences on adiposity.

Limitations

The twin method is based on two main assumptions. The first is that MZ twins and DZ twins will have equally similar environments; this is one of the benefits of studying DZ twins and not just ordinary siblings. This assumption, termed the “equal environments assumption” (25), means that greater MZ phenotypic similarity is attributed to genetic influence. However if it is the case that MZ twins experience more similar environments than DZ twins, then phenotypic similarity may be due to environmental and not genetic influences. Much research has tested the equal environments assumption (26) and although

there is evidence to suggest that MZ twins are treated more similarly (27), this does not appear to significantly affect twin similarity (28). The second assumption of the twin method is that results from twin studies can be generalized to the rest of the population. There are ways in which twins have been found to differ from singletons (25); for example, twins on average have lower birth weights and are often born 3–4 weeks prematurely (14). However, studies on older twins indicate that these differences have all but disappeared by early to middle childhood (25). Further discussion of the assumptions of the twin method can be found elsewhere (13,14,29). A specific limitation of this study is the use of parental reports of children's heights and weights, although previous research has shown that they are reasonably reliable (30). This was confirmed in our sample on a subsample at 10 years: Home measurements of height and weight, taken by trained researchers, correlated 0.83 and 0.90, respectively, with parental report.

As with all longitudinal studies, there is attrition over time, and this was exaggerated in the response rate for the 10-year data because we contacted families who were not currently active participants in TEDS, as well as the active families. It is possible that families with extremely obese children were less likely to respond, and this is of course a limitation of the study, and therefore we cannot rule out the possibility of a different pattern of results for extremely obese cases if they were not included in these analyses. The most likely impact of attrition is only to reduce the size of the sample, and therefore the consequent statistical power, and fortunately TEDS is a very large study and we had a reasonable number of probands to assess the links between the extreme and the rest of the distribution. Ultimately, all of the findings will be empirically testable once specific genetic and environmental determinants have been identified.

It would have been beneficial to collect additional measures of adiposity such as body fat mass, but this was not feasible on such a large sample. In future, more intensive studies, we plan to examine genetic and environmental covariation between BMI and alternative measurements of adiposity.

Finally, we were not able to include specific measurements of the environment in this study. We believe that there are many environmental factors that influence BMI. It would be beneficial in future studies to include such measurements to test whether there are indications of gene–environment correlations and gene–environment interactions.

Implications

Our results support the view that obesity is the quantitative extreme of the genetic and environmental influences that operate across the distribution of BMI. In other words, common obesity is not a disorder that is etiologically distinct from normal BMI, and while diagnostic cutoffs have clinical value, they may be arbitrary in relation to etiology.

One implication of this finding concerns attempts to identify genes responsible for the high heritability of obesity. Bell *et al.* (2) hypothesized that there would be minimal overlap between genes for normal weight and those for

obesity—however, our research indicates that there is likely to be substantial overlap. Quantitative trait loci associated with obesity will also be associated with BMI variation throughout the normal distribution and vice versa. In other words, genes associated with obesity are not genes “for obesity”—they are genes predisposing to greater adiposity. Even in pairs of siblings with low BMIs, the sibling with more “obesogenic alleles” will be heavier. Likewise, environmental influences should be similar across the distribution.

A second implication is that clinicians should be aware that obesity is strongly influenced by genetic factors, and respond to patients (or in the case of childhood obesity, parents) appropriately. Awareness that genes are important in determining weight can reduce the burden of blame on the parents or the child. But it is also important to stress that strong genetic influence does not imply that environmental interventions cannot work, but rather that weight control is likely to be more difficult for children who have more than the average complement of “weight gain” quantitative trait loci.

In summary, obesity is not a disorder that is etiologically distinct from normal variation in BMI. Our findings indicate that for obesity in childhood, the abnormal is normal.

ACKNOWLEDGMENTS

We gratefully acknowledge the ongoing contribution of the parents and children in the Twins' Early Development Study. The Twins' Early Development Study is supported by a program grant (G0500079) from the UK Medical Research Council and the work on obesity in the Twins' Early Development Study is supported in part by a grant from the Biotechnology and Biological Sciences Research Council (31/D19086).

DISCLOSURE

The authors declared no conflict of interest.

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