Genetic determinants of eating disorders

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Chapter 4

Genetic influences on disordered eating behavior are largely independent of BMI

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Abstract

Introduction: Prior studies suggest eating disorders and related characteristics are moderately to substantially heritable. We are interested in identifying genes underlying disordered eating behavior (DEB), and want to know how much of the genetic influence underlying DEB is attributable to genetic influences on BMI.

Method: Bivariate analyses were performed, in adolescent twins and siblings from the Netherlands Twin Registry, to estimate the genetic and environmental contributions for DEB, BMI and their overlap.

Results: Shared genetic risk factors explained the overlap between BMI and DEB (genetic correlation was 0.43 in women, 0.51 in men). DEB was highly heritable in women (a^2=0.65; a^2 independent of BMI=0.53) and moderately heritable in men (a^2=0.39; a^2 independent of BMI=0.29). BMI was highly heritable in both men (a^2=0.76) and women (a^2=0.80).

Conclusion: The entire correlation between DEB and BMI was explained by shared genetic risk, but the majority of genetic influences on DEB were due to genetic effects independent of BMI.

Despite substantial efforts to identify causal pathways for anorexia and bulimia nervosa, very little is known about the aetiology of eating disorders. In longitudinal and cross-sectional studies, several risk factors have been identified, including gender, elevated weight and shape concerns, negative body image, negative self-evaluation, dieting and childhood obesity (Jacobi et al., 2004).

Various family and twin studies have been performed to explore causes of individual differences in the development and stability of eating disorders, a variety of eating disorder symptoms, and related characteristics. In population-based twin studies, the heritability estimates for these different phenotypes in women ranged from zero to 0.82, but on average a moderate heritability of around 0.40 was estimated (Bulik et al., 1998; Bulik et al., 2003b; Bulik et al., 2006; Holland et al., 1988; Keski-Rahkonen et al., 2005; Klump et al., 2000; Klump et al., 2003; Neale et al., 2003a; Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud et al., 2004b; Reichborn-Kjennerud et al., 2004a; Rowe et al., 2002; Rutherford et al., 1993; Slof-Op 't Landt et al., 2005; Sullivan et al., 1998a; Wade et al., 1998). In men, heritability estimates ranged from 0 to 0.51, with an average heritability estimate of 0.20 (Keski-Rahkonen et al., 2005; Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud et al., 2004b; Reichborn-Kjennerud et al., 2004a; Rowe et al., 2002). Only one study focussed on the overlap between eating attitudes, behavior and body weight in adolescent female twins (Klump et al., 2000). This is an interesting overlap to investigate, since body weight might be a risk factor for the development of eating disorders (Jacobi et al., 2004).

We herein report the results of a bivariate twin study on disordered eating behavior (DEB) and body mass index (BMI) in a Dutch population sample of adolescent male and female twins. To overcome the drawbacks and limitations of the previous studies (such as small sample sizes, inadequate power, and the use of categorical data; e.g. see (Slof-Op 't Landt et al., 2005, review)), we used a large sample of twins and siblings aged 11-18 years. DEB was measured in a more continuous fashion. Four items on different eating disorder features were used to calculate a sum score. Three items used in this study are based on eating disorder criteria from the DSM-IV (1994). The fourth item, dieting, was added to assess an important risk factor for the development of eating disorders (Jacobi et al., 2004). Prior work has shown that these four items could be accounted for by one underlying latent factor in a confirmatory factor analysis (Slof-Op 't Landt et al., 2009). However, the DEB items were not measurement invariant with respect to sex, indicating that this scale might not measure the same trait in men and women (Slof-Op 't Landt et al., 2009). Therefore the genetic analyses were performed separately in men and women.

The aim of the current study is to investigate how much of the heritability in DEB is attributable to genetic effects on body mass index (BMI), and how much of it is independent of these effects. Because we would like to identify genes that influence DEB in the future, investigating the overlap between DEB and BMI may shed some light on possible biological pathways involved in DEB. We performed a bivariate analysis using both traits, to estimate the overlap between DEB and BMI and to disentangle the proportion of variance due to shared and specific genetic and environmental factors.

Materials and methods

Sample

All participants were registered with the Netherlands Twin Registry (NTR), kept by the Department of Biological Psychology at the VU University in Amsterdam. Young twins (YNTR) are registered at birth by their parents, who are approached through 'birth felicitation' services. During the first years of their lives the parents are the primary sources of information on their development. Twins are categorized by birth cohort and data collection is cohort driven. Nationwide data collection of all families is by mailed surveys. Parents of twins receive questionnaires when their twins are aged 1, 2, 3, 5, 7, 10, and 12 years of age. At ages 7, 10, and 12, teacher data are also collected, after written permission is given by the parents. When the twins are 14, 16, and 18 they receive a self report questionnaire, used in the current study (Bartels et al., 2007; Boomsma et al., 2006). For this study data from the 1986-1992 birth cohorts were used. In January 2005, questionnaires were sent to 14-, 16- and 18-year old twins and their non-twin siblings. The twins and siblings were asked to complete a survey containing items relevant for eating disorders. Questionnaires were sent to 2000 families. A total of 2131 twins and 517 siblings from 1121 families returned the questionnaire (family response rate 56.1 %).

Zygosity was determined for 461 same-sex twin pairs by DNA analysis or blood group polymorphisms. For all other same-sex twin pairs, zygosity was determined by discriminant analysis, using longitudinal questionnaire items. Agreement between zygosity assignment by the replies to the longitudinal questionnaire and zygosity determined by DNA markers/blood typing was around 93% (Rietveld et al., 2000).

The final sample consisted of 474 monozygotic twin pairs (194 male (MZM) and 280 female (MZF) pairs), 310 dizygotic twin pairs (140 male (DZM) and 170 female (DZF) pairs), and 45 incomplete twin pairs (22 men and 23 women). The sibling group was comprised of 69 brothers and 115 sisters.

Measures

The Dutch Health Behaviour Questionnaire is a self-report instrument containing direct measures of several health and behavior features, including a number of eating disorder characteristics and self report of height and weight. Based on the self-reported height and weight, the body mass index (BMI = weight [kg] / height^2 [m]) was used as a measure of relative body weight in this study.

The eating disorder section included four items: 1) dieting (have you ever gone on a diet to loose weight or to stop gaining weight?); 2) fear of weight gain (how afraid are you to gain weight or become fat?); 3) importance of body weight or shape on self-evaluation (how important are body weight and/or shape in how you feel about yourself?); 4) eating binges (have you ever had eating binges?). Responses were given on a five point scale. The scores on the four items were summed to calculate disordered eating behavior (DEB). If one of the four eating disorder items was missing, the sum score was also missing.

Prior work has shown that these four items could be accounted for by one underlying latent factor in a confirmatory factor analysis (Slof-Op 't Landt et al., 2009). In comparing groups or parallel use of data from different groups, such as men and women, it is important that an instrument measures the same underlying latent (unobserved) trait in these groups. Observed group differences in the sum scores should accurately reflect group differences with respect to the latent variable. A necessary condition for this is that the instrument displays measurement invariance with respect to the groups under consideration (Mellenbergh, 1989; Meredith, 1993). Formally, measurement invariance requires that the distribution of the item scores, conditional on only the trait score equals the distribution of the item scores, conditional on both the trait score and group membership. If for example men score lower on average on one item than women without actually scoring lower on the total scale (underlying trait), this item is said to lack measurement invariance. In that case, observed group differences in sum scores might not be caused by true differences in the underlying trait, but by measurement bias. Prior analyses have shown that the four eating disorder items were not measurement invariant with respect to sex. This implies that the sum score based on these items cannot be taken to present exactly the same trait in men and women. Therefore all analyses were performed separately in men and women.

Statistical Analyses

Age-effects for both DEB and BMI were expected (Klump et al., 2000; Schousboe et al., 2003), therefore we first calculated the correlations between both traits and age in the two sex groups. For the descriptive statistics, we tested whether the means and variances for DEB and BMI were equal between the twins and siblings in men and women.All analyses were performed using the software package Mx (Neale et al., 2003b). The means were corrected for age in all genetic analyses.

In the next step, the phenotypic correlation between DEB and BMI was calculated. Subsequently we calculated twin correlations, twin-sibling, and cross-twin/sib cross- trait correlations. The correlations provide an initial indication of genetic and environmental effects on DEB, BMI, and their overlap. By constraining the DZ twin correlations and the twin-sib correlation to be equal the presence of a specific twin environment is tested. Monozygotic (MZ) twin pairs are genetically (nearly) identical, whereas dizygotic twin and sibling pairs share on average 50% of their segregating genes. Therefore, if the MZ twin correlation is substantially larger than the DZ twin and twin-sib correlations genetic influence is implied. Shared family environmental factors (for example religion, socioeconomic level and parenting style) will make family members relatively more similar and will create differences between families. If the MZ and DZ twin correlation are similar and both statistically significant, shared environmental influence is suggested. Finally, the importance of non-shared environmental influences can be seen from the extent to which the MZ twin correlations differ from one. This influence stands for the impact of all environmental factors influencing only one of the twin pair (for example illness, trauma or relationships with peers). In addition, the pattern of cross-twin cross-trait correlations for MZ twins and DZ twins and siblings indicates to what extent the covariance between the traits is influenced by genetic or environmental components. Finally, if a twin specific environment is implied if DZ twin correlations are significantly higher than twin-sib correlations.

The Cholesky Decomposition or triangular decomposition, is used for the bivariate genetic model fitting. The Cholesky decomposition decomposes the phenotypic statistics into genetic, shared environmental, and nonshared environmental contributions. In other words the pattern of the factor loadings on the latent genetic and environmental factors reveals a first insight into the etiology of covariances between DEB and BMI. Since the saturated model is fully parameterized, it yields the best possible fit to the input matrices.

The bivariate Cholesky decomposition model contained two latent factors for A, C and E respectively (per individual), of which the variances were constrained to be one. In Figure 4.1 the path diagram of this model is shown. Correlation coefficients are represented by curved lines with an arrow at each end. Within a twin- or sibling pair the C component for a trait is identical for each member (correlation coefficient of one), the E component is uncorrelated. A on the other hand, is identical for MZ twins but the correlation is 0.5 for DZ twins or sibling pairs. BMI loaded on the first latent factors A, C and E.

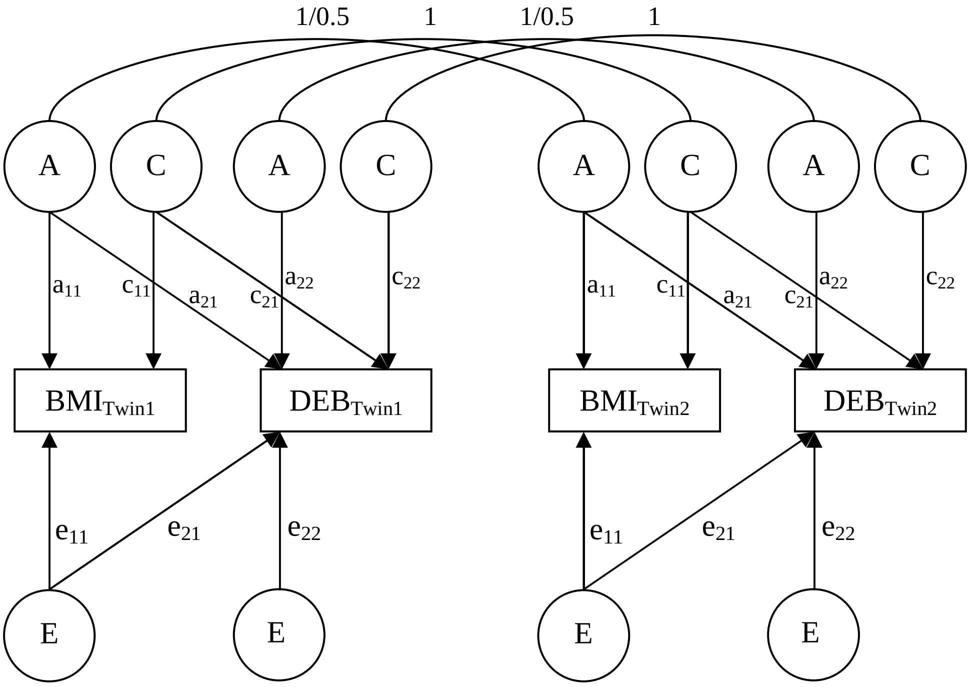

Figure 4.1. The bivariate Cholesky model for BMI and DEB, represented for a twin or sibling pair. Correlation coefficients are represented by curved lines with an arrow at each end. Variance in each phenotype is assumed to be determined by the additive combination of three latent factors: additive genetic effects (A), shared environmental effects (C) and nonshared environmental effects (E). BMI loaded on the first latent factors A, C and E. The additive genetic, shared environmental and nonshared environmental variance in DEB scores are partitioned into those components attributable to the genetic and environmental effects on BMI (a_{21}, c_{21}, e_{21}) and residual components that are independent of the genetic and environmental effects of BMI (a_{22}, c_{22}, e_{22}).

The phenotypic variance for BMI is represented by the sum of squared estimates of factor loadings (i.e., (a_{11}^2) + (c_{11}^2) + (e_{11}^2)). DEB loaded on both factors, and the sum of the squared factor loadings (i.e., ($a_{21}^2 + a_{22}^2$) + ($c_{21}^2 + c_{22}^2$) + ($e_{21}^2 + e_{22}^2$)) represented the phenotypic variance for this trait. The heritability of BMI and DEB will be estimated by:

$$a^2_{BMI} = a_{11}^2 / (a_{11}^2 + c_{11}^2 + e_{11}^2)$$
$$a^2_{DEB} = (a_{21}^2 + a_{22}^2) / (a_{21}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{21}^2 + e_{22}^2)$$

When multiplying the factor loadings on the first latent factors (i.e., (a_{11} x a_{21}) + (c_{11} x c_{21}) + (e_{11} x e_{21})), the covariance between BMI and DEB is derived. Based on the covariance, genetic and environmental correlations between the two traits can be calculated (see below).

$$\text{Genetic correlation: } r_g = (a_{11} \text{ x } a_{21}) / (\sqrt{}a_{11}^2 \text{ x } \sqrt{}(a_{21}^2 + a_{22}^2)$$
$$\text{Common environmental correlation: } r_c = (c_{11} \text{ x } c_{21}) / (\sqrt{}c_{11}^2 \text{ x } \sqrt{}(c_{21}^2 + c_{22}^2)$$
$$\text{Unique environmental correlation: } r_e = (e_{11} \text{ x } e_{21}) / (\sqrt{}e_{11}^2 \text{ x } \sqrt{}(e_{21}^2 + e_{22}^2)$$

Based on the estimated heritability for DEB and the genetic correlation, the heritability estimates for DEB dependent on BMI (a_{21}^2) and independent on BMI (a_{22}^2) can be determined by:

$$a_{21} = r_g \text{ x } (a_{21} + a_{22}) = rg \text{ x } a_{DEB}$$
$$a_{22} = a_{DEB} - (rg \text{ x } a_{DEB})$$

We fitted models by the method of maximum likelihood to data from all twins and siblings, separately in women and men, beginning with a full bivariate ACE model. Subsequently, parameters (a_{21}, c_{21}, e_{21},) were dropped from the model to test if the covariance between traits can be attributed to shared genes (a_{21},) or overlapping C or E influences. Twice the difference in log-likelihood between two models yields a statistic that is asymptotically distributed as a Chi-square statistic with degrees of freedom equal to the difference in the number of estimated parameters in the two models. This statistic can be used to test the tenability of the constraints associated with the more constrained model. According to the principle of parsimony, models with fewer estimated parameters are preferred if they do not give a significant deterioration of the fit ($p>0.05$)..

Based on the twin and twin-sibling correlations estimated in this study, we performed power analyses in Mx. We calculated the power to test for the significance of the different paths of A (a_{11},a_{21},a_{22}) and/or C (c_{11},c_{21},c_{22}) in a bivariate model with a significance level α of .05 for the phenotypes (DEB and BMI). In addition, we calculated the statistical power to test whether the genetic correlation between the two phenotypes was statistically different from one or zero in the bivariate model. A genetic correlation of one indicates that identical genes are underlying the genetic influence on the traits. A genetic correlation of zero, means that genetic influences on the traits are totally independent from each other. This analysis was based on the results of the full bivariate model.

Results

Based on the independent analyses in women and men, results for women and men are presented separately.

Table 4.1 Descriptive statistics for DEB and BMI in women (upper part) and men (lower part) per zygosity

	DEB					BMI				
	N	Mean[a]	Var	Min	Max	N	Mean[a]	Var	Min	Max
Women										
MZF firstborn	280	8.0	6.1	4.0	18.0	266	20.1	8.4	14.2	34.6
MZF second born	278	7.7	6.2	4.0	17.0	268	19.7	7.7	14.7	36.4
MZF sister	64	8.2	5.5	4.0	16.0	61	20.9	8.8	14.0	30.8
DZF firstborn	172	7.9	5.7	4.0	16.0	169	20.3	8.3	14.5	32.7
DZF second born	173	7.9	6.1	4.0	19.0	169	20.2	7.9	15.5	33.2
DZF sister	49	8.1	7.8	4.0	15.0	47	20.5	8.3	13.7	29.9
Men										
MZM firstborn	194	6.3	3.4	4.0	13.0	183	20.0	8.4	13.0	34.0
MZM second born	190	6.3	3.4	4.0	12.0	190	19.7	6.5	14.1	34.0
MZM brother	41	6.6	4.6	4.0	14.0	40	20.9	8.2	16.2	34.6
DZM firstborn	145	6.5	3.0	4.0	13.0	140	19.7	5.6	15.1	30.3
DZM second born	141	6.3	2.5	4.0	12.0	139	19.3	3.9	13.8	26.2
DZM brother	26	**5.7**[b]	2.0	4.0	10.0	26	**21.2**[b]	5.9	15.7	28.4

MZF = monozygotic females, DZF = dizygotic females

MZM= monozygotic males, DZM= dizygotic males

[a] Unadjusted means, in the analyses means were adjusted for age

[b] The mean for both DEB and BMI of the DZM brothers was not equal to the means in the remaining males.

Women

In the women both BMI and DEB showed a significant correlation with age, r=0.27 (95% CI 0.19-0.34) and r=0.14 (95% CI 0.06-0.21) respectively. BMI and DEB scores increased with increasing age. The descriptive statistics for the female sample are presented in the upper part of Table 4.1. Means (adjusted for age), and variances of DEB and BMI were equal in the female twins and siblings ($\chi^2_8 = 5.54$; *p*= 0.70). The phenotypic correlation between BMI and DEB was 0.32 (95% CI 0.25-0.38) in women. Table 4.2 displays the correlations and cross-correlations for BMI and DEB in MZ twins, and same-sex DZ twins/twin-sibling pairs in the women. All the MZ correlations, both cross-twin and cross-twin cross-trait, were substantially higher than the DZ/twin-sibling correlations. In other words, genetic influence is implied in DEB, BMI, and the overlap between these traits. DZ twin correlations and twin-sibling correlations could be constrained to be equal ($\chi^2_{18} = 26.72$; *p*= 0.08).

Table 4.2 Correlations and cross-correlations for DEB and BMI in monozygotic twins, and in same-sex dizygotic twins or twin-sibling pairs. Women are presented in the upper part of the table, men in the lower part.

		MZ		DZ / same-sex siblings	
		DEB	BMI	DEB	BMI
Women	DEB	**0.67** (0.60, 0.72)		**0.21** (0.10, 0.32)	
	BMI	*0.29* (0.20, 0.37)	**0.80** (0.76, 0.84)	*0.15* (0.07, 0.24)	**0.30** (0.19, 0.40)
Men	DEB	**0.38** (0.26, 0.49)		**0.25** (0.12, 0.37)	
	BMI	*0.24* (0.15, 0.33)	**0.76** (0.70, 0.81)	*0.23* (0.13, 0.32)	**0.34** (0.21, 0.45)

95% confidence intervals are shown in parentheses

In Table 4.3, the parameter estimates and fit statistics for the full model and the best-fitting model, from the bivariate twin analyses, are presented. The AE model, with genetic influences explaining the overlap between BMI and DEB (a_{21}) gave the best fit to the data. Both BMI and DEB were highly heritable in women. The total phenotypic correlation between BMI and DEB was due to shared genetic influences with an r_g of 0.43 (95% CI 0.34- 0.52) in women.

Table 4.3 Fit statistics and parameter estimates of the full and best-fitting model of bivariate Cholesky analysis of BMI and DEB in female same-sex twins and siblings.

	Fit statistics			
	$-2ll^{a}$	df	$\Delta\chi^{2\ b}$	$\Delta df^{\ c}$
ACE; a_{12}, c_{12}, e_{12}	9034.13	1983	-	-
AE; a_{12}	**9035.54**	**1987**	**1.42**	**4**

	a^2		c^2		e^2	
	BMI	DEB	BMI	DEB	BMI	DEB
ACE;	0.80	0.65	0.00	0.00	0.20	0.35
a_{12}, c_{12}, e_{12}	(0.71, 0.84)	(0.55, 0.71)	(0, 0.08)	(0, 0.08)	(0.16, 0.25)	(0.29, 0.42)
AE; a_{12}	**0.80**	**0.65**	**-**	**-**	**0.20**	**0.35**
	(0.75, 0.84)	**(0.58, 0.71)**			**(0.16, 0.25)**	**(0.29, 0.42)**

95% confidence intervals shown in parentheses

[a] -2ll: -2 log likelihood

[b] $\Delta\chi^2$: Chi-square test statistic between two models

[c] Δdf: degrees of freedom for the Chi-square difference test

For the women, the statistical power to test for the significance of the different paths of A (a_{11},a_{21},a_{22}) was 1.00 in the bivariate analyses. In addition, the power to test whether r_g

was significantly different from zero or one, was also 1.00. This means that we had sufficient power to decompose the variance and covariance in BMI and DEB.

Men

The correlation between age and BMI was 0.35 (95% CI 0.26-0.42) in men, between age and DEB a non significant correlation of 0.08 (95% CI -0.01-0.16) was obtained. In the lower part of Table 4.1, the descriptive statistics for the male sample are listed. Not all means of DEB and BMI were equal between twins and siblings. The mean of DEB was lower, while the mean of BMI was higher in the DZM brothers compared to the other male twins and siblings ($\chi^2_6 = 8.33$; $p = 0.22$). In the subsequent analyses, we therefore used different means for the DZM brothers.

The phenotypic correlation between BMI and DEB was 0.28 (95% CI 0.21-0.36). The lower part of Table 4.2 displays the correlations and cross-correlations for BMI and DEB in MZ twins, and same-sex DZ twins or twin-sibling pairs estimated in the male sample. The correlations for BMI and DEB were substantially higher in the MZ than in the DZ/twin-sibling pairs in men. The cross-twin cross-trait correlation, however, was quite similar in the MZ and DZ/twin-sibling pairs. DZ twin correlations and twin-sibling correlations could be constrained to be equal ($\chi^2_{18} = 26.52$; $p = 0.09$).

Table 4.4. Parameter estimates and fit statistics of the full and best-fitting model of bivariate Cholesky analysis of BMI and DEB in male same-sex twins and siblings.

	Fit statistics					
	-2ll[a]	df	$\Delta\chi^2$ [b]	Δdf [c]		
ACE; a_{12}, c_{12}, e_{12}	6023.62	1440	-	-		
AE; a_{12}	**6026.35**	**1444**	**2.72**	**4**		
	a^2		c^2		e^2	
	BMI	DEB	BMI	DEB	BMI	DEB
ACE;	0.69	0.21	0.07	0.16	0.24	0.35
a_{12}, c_{12}, e_{12}	(0.52 0.79)	(0.00, 0.45)	(0, 0.23)	(0, 0.37)	(0.19, 0.30)	(0.29, 0.42)
AE; a_{12}	**0.76**	**0.39**	**-**	**-**	**0.24**	**0.35**
	(0.70, 0.81)	**(0.28, 0.49)**			**(0.19, 0.30)**	**(0.29, 0.42)**

95% confidence intervals shown in parentheses

[a] -2ll: -2 log likelihood

[b] $\Delta\chi^2$: Chi-square test statistic between two models

[c] Δdf: degrees of freedom for the Chi-square difference test

For the bivariate Cholesky decomposition analyses, the AE model with genetic components explaining the overlap (a_{21}), gave the best fit to the data. In Table 4.4, the parameter estimates as well as the fit statistics are mentioned for the full and best-fitting models in the male sample. DEB was moderately heritable in men, whereas BMI was a highly heritable trait. The total phenotypic correlation between BMI and DEB was due to shared genetic influences with an r_g of 0.51 (95% CI 0.37-0.64) in men.

The statistical power to test for the significance of the different paths of A (a_{11},a_{21},a_{22}) was 1.00 in the male sample. However, the power to test whether r_g between BMI and DEB was statistically different from one was only 0.58, while the power to test if r_g was significantly different from zero was 0.99 in the AE model. This means, that we had limited power to estimate the size of r_g accurately.

How much of the genetic influence on DEB is independent of BMI?

In both women and men the estimated genetic correlations indicated that about half of the genetic factors that influence BMI also influence DEB. But what does this mean for the heritability? How much of the heritability estimate in DEB is attributable to genetic influences on BMI, and how much is independent of it? Based on the genetic correlation we can calculate the heritability of DEB independent of genetic influences on BMI. For women this leads to a heritability estimate of 0.53, in the men an independent heritability of 0.29 was obtained. These results show that the majority of genetic influence on DEB is independent of genetic influences on BMI.

Discussion

Twin-, cross-twin, and twin-sibling correlations indicated that a large part of the variance in both DEB and BMI was explained by genetic factors, and that genetic components were underlying the overlap between DEB and BMI in women. The bivariate analysis showed that DEB is a highly heritable trait in women (a^2=0.65) and moderately heritable in men (a^2=0.39), whereas BMI is highly heritable in both women (a^2=0.80) and men (a^2=0.76). In addition, additive genetic factors were responsible for the total overlap between the two characteristics, yielding a genetic correlation of 0.43 in women and 0.51 in men. Despite the overlap between BMI and DEB, the majority of the genetic influences on DEB were due to genetic effects that are independent of BMI in women as well as men.

Klump et al. (2000) used a bivariate Cholesky decomposition analysis to examine the genetic and environmental contributions to BMI and several scales from the Eating Disorder Inventory (EDI) in adolescent female twins. In this study heritability estimates ranged from 0.02 to 0.45 in 11-year old twins, and 0.52 to 0.63 in 17-year old twins for the EDI scales, and from 0.78 to 0.84 for BMI in both 11-year and 17-year old twins. Genetic correlations between 0.38 and 0.97 in 11-year old twins and between 0.33 and 0.60 in 17-year old twins were estimated for BMI and the different scales of the EDI. Despite the difference in age and the use of different assessment instruments, our results in the women were comparable to the estimates in the 17-year old twins from this study. In addition, results from the current study are comparable to adult population-based univariate twin studies that have investigated genetic and environmental contributions to BMI (Schousboe et al., 2003), and eating disorder related characteristics (Bulik et al., 1998; Bulik et al., 2003b; Bulik et al., 2006; Holland et al., 1988; Keski-Rahkonen et al., 2005; Klump et al., 2000; Klump et al., 2003; Neale et al., 2003a; Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud et al., 2004b; Reichborn-Kjennerud et al., 2004a; Rowe et al., 2002; Rutherford et al., 1993; Sullivan et al., 1998a; Wade et al., 1998).

The majority of the variance in DEB was explained by genetic factors in women, while unique environmental factors had the largest influence in men. Since eating disorders are more common in women, items used to asses symptoms and features related to these disorders are also mainly developed for women. The scale we used might not be measuring the same underlying trait in men and women (Slof-Op 't Landt et al., 2009), the differences in heritability estimates between the sexes in the current study can therefore be indicative of a true difference in disordered eating behavior, but might also be due to measurement bias. None of the previously performed twin studies examining eating disorder related characteristics (Keski-Rahkonen et al., 2005; Reichborn-Kjennerud et al., 2003; Reichborn-Kjennerud et al., 2004b; Reichborn-Kjennerud et al., 2004a; Rowe et al., 2002) in both men and women, have tested whether the items used to asses the phenotype measured the same trait in both sexes. As a consequence it is not clear if the reported differences and similarities between male and female heritability estimates are due to measurement bias or true sex differences in disordered eating behavior.

The genetic correlation of 0.43 in women and 0.51 in men obtained in this study, indicates that approximately 50% of the genetic factors that influence BMI also influence DEB. Because DEB and BMI are related with each other, it would be interesting to disentangle the direction of causation of the overlap between these characteristics. Genetic influences on for example metabolism may be causal to weight gain that eventually leads to disturbed eating behavior. Genetic influences on DEB may alternatively be causal to a disturbed eating profile, leading to fluctuations in weight. Eventually we would like to identify genes that are underlying DEB. Therefore, we are planning to test the causal hypothesis in future studies, to further clarify the underlying aetiology of the overlap between BMI and DEB. Several approaches can be taken to disentangle the direction of causation, for example phenotypic causation models (Duffy & Martin, 1994; Heath et al., 1993) and the co-twin control design (Cederlof et al., 1977; Kendler et al., 1993). The first method is a nested model of the bivariate Cholesky decomposition, in this approach the correlated traits need to have different modes of inheritance. In the co-twin control design relative risks for DEB would be compared between unrelated individuals discordant for BMI, DZ twins discordant for BMI, and MZ twins discordant for BMI.

The power analysis revealed that our sample size was sufficient to detect genetic and shared environmental effects on BMI and DEB (both dependent and independent from BMI) in men and women. Our female sample size also was sufficient to estimate the genetic correlation between BMI and DEB correctly. In the men, we had limited statistical power to estimate this correlation. The small difference between the cross-twin cross-trait correlations in the male MZ and DZ/twin-sib pairs gave a first indication for this lack of power. As a consequence, there is a possibility that the overlap between BMI and DEB is not solely due to genetic factors in men, but that common environmental factors also play a role.

A concern with regard to our study is the selection of the eating disorder features, and the comparability of this phenotype with other studies. Three items used in this study are based on DSM-IV (1994) criteria for eating disorders. The fourth item, dieting, was added to assess an important risk factor for the development of eating disorders (Jacobi et al., 2004). Within the eating disorder field a broad variety of assessment instruments is used to assess eating disorders and eating disorder-related phenotypes. A majority of these assessment instruments is based on DSM-IV criteria, indicating that our broad phenotype is probably fairly comparable to these phenotypes. However, one eating disorder symptom is missing in our phenotype, namely compensatory behavior. Heritabilities of 0.50 for compensatory behavior in 17-year old female twins (Klump et al., 2000) and 0.70 for self-induced vomiting in adult female twins (Sullivan et al., 1998a) have been found. Based on these findings, the inclusion of compensatory behaviors in our phenotype might not influence the results found for the women in the current study. However, we do not know what the consequences for the heritability estimates in the men would be, especially since significant gender differences have been reported for a variety of compensatory behaviors like self-induced vomiting, laxative use and fasting (Anderson & Bulik, 2004).

The current study provides further evidence that genetic components are underlying disordered eating behavior in both men and women. Part of these genetic components are influencing both BMI and disordered eating behavior, while the majority of genetic effects influencing disordered eating behavior is independent of the genetic effects that influence

BMI. In future studies, we hope to identify genes that are involved in this eating disorder phenotype by performing genetic association studies.