Psychological Medicine, 2001, **31**, 737–740. Printed in the United Kingdom

BRIEF COMMUNICATION

Genetic and environmental influences on anorexia nervosa syndromes in a population–based twin sample

K. L. KLUMP,[1] K. B. MILLER, P. K. KEEL, M. McGUE AND W. G. IACONO

From the Department of Psychology, Michigan State University, East Lansing, MI; Department of Psychology, University of Minnesota, Minneapolis, MN; and Department of Psychology, Harvard University, Boston, MA, USA

ABSTRACT

Background. Genetic and environmental influences on broadly-defined anorexia nervosa (AN) syndrome were examined in a population-based twin sample.

Methods. AN syndrome was assessed in 672 female 17 year-old twins using structured interviews and a self-report questionnaire.

Results. Twenty-six probands with AN syndrome were identified. Biometrical model-fitting analyses indicated that genetic and non-shared environmental factors accounted for 74% and 26% of the variance in AN syndrome, respectively.

Conclusions. Findings support previous research indicating significant genetic and non-shared environmental influences on AN syndromes.

INTRODUCTION

Family studies have indicated that the prevalence of eating disorders is seven to 12 times higher in relatives of anorexic probands compared with controls (Lilenfeld *et al.* 1998; Strober *et al.* 2000). Higher concordance rates among monozygotic (MZ) relative to dizygotic (DZ) twins have suggested genetic influence on the observed familiality (Holland *et al.* 1984, 1988; Treasure & Holland, 1990). However, heritability estimates have ranged from 0% to 80% for anorexia nervosa (AN) (Holland *et al.* 1984, 1988; Treasure & Holland, 1990; (Walters & Kendler, 1995; Wade *et al.* 2000), with non-shared environmental influences accounting for the remaining variance (Wade *et al.* 2000). Discrepant heritability estimates may be due to small sample sizes (Holland *et al.* 1984, 1988; Treasure & Holland, 1990; Walters & Kendler, 1995; Wade *et al.* 2000), changes in zygosity assignment (Walters & Kendler, 1995; T. D. Wade, personal communication, August 2000) or differences in findings from clinical (Holland *et al.* 1984, 1988; Treasure & Holland, 1990) *versus* population-based samples (Walters & Kendler, 1995; Wade *et al.* 2000). Inconsistent results highlight the need for additional population-based twin studies to clarify findings and determine the generalizability of heritability estimates from clinical samples.

A limitation of past research is the lack of independent samples. Three of the most commonly cited studies of AN share approximately 22% of their samples (Holland *et al.* 1984, 1988; Treasure & Holland, 1990). In addition, population-based twin studies of AN are based on only one cohort (Walters & Kendler, 1995; Wade *et al.* 2000). Independent replications of genetic effects are needed to appreciate the magnitude of genetic influences on these disorders.

[1] Address for correspondence: Dr Kelly L. Klump, Department of Psychology, Michigan State University, 129 Psychology Research Building, East Lansing, MI 48824, USA.

The primary aim of the current study was to examine genetic and environmental influences on AN syndromes in a longitudinal, population-based sample of adolescent twins.

METHOD

Participants

The sample comprises 672 reared-together female twins ages 16 to 18 years (mean = 17·46 years, S.D. = 0·51) drawn from the longitudinal, population-based Minnesota Twin Family Study (MTFS). Recruitment procedures and study methodology have been described previously (Iacono *et al.* 1999). Zygosity was established using standard questions, a trained research assistant's evaluation of twin physical similarity, and an algorithm diagnosis calculated from ponderal index, cephalic index and fingerprint ridge count. Disagreements among these indices were resolved through serological examination of 12 blood group antigens and protein polymorphisms. In a validation study of 50 pairs, when the three zygosity estimates agreed, serological analyses confirmed the agreement in every case. After complete description of the study to participating subjects, written informed consent was obtained.

Measures

AN diagnoses were assessed with the Eating Disorders Structured Clinical Interview (EDSCI). The EDSCI is based on the eating disorders module of the Structured Clinical Interview of DSM-III-R (Spitzer *et al.* 1987) and was modified to assess DSM-III-R and DSM-IV AN in older as well as younger (i.e. 11-year-old) subjects. Twin responses to a 30-item version (Klump *et al.* 2000) of the Eating Disorder Inventory (EDI) (Garner *et al.* 1983) were also used to validate diagnoses.

Diagnostic procedures

Interviews were conducted in-person and blind to zygosity. An AN broad phenotype was examined in order to maximize statistical power. The use of broader phenotypes is supported by studies showing that subthreshold cases of AN lie on a continuum of liability with full eating disorders (Walters & Kendler, 1995; Strober *et al.* 2000).

Three DSM-IV AN diagnostic categories were examined. Subjects were included in the 'threshold' category if they were below 85% of ideal body weight (IBW) and met all criteria for AN or fell one symptom short. Subjects were included in the 'subthreshold AN' category if they were $\leqslant 90\%$ of IBW, they met criteria for at least one cognitive symptom of AN (i.e. intense fear of weight gain OR disturbance in perception of body size and shape), and they scored above the mean (11·0) for all twins with 'threshold' eating disorders on the EDI. Finally, a third category comprising both the 'threshold' and 'subthreshold' subjects ('AN syndrome') was included in analyses to obtain genetic estimates within a larger sample of twins.

The kappa coefficient between two independent diagnostic teams for AN diagnoses was adequate (kappa = 0·63). In addition, consensus meeting reviews of diagnoses by eating disorder specialists (K.L.K., K.B.M., P.K.K.) and validation using EDI scores further supported the integrity of the diagnoses.

Statistical analyses

Statistical tests were conducted only for the 'Syndrome' category due to the small number of subjects in the other diagnostic groups. Probandwise concordance was computed using $2C/(2C+D)$ where C is the number of pairwise concordant and D is the number of discordant twin pairs (McGue, 1992). Structural equation models were fit to twin tetrachoric correlations using the maximum-likelihood method and the Mx software program (Neale, 1995). These analyses were used to estimate the relative contribution of additive genetic (A), shared environmental (C) and non-shared environmental (E) influences to eating pathology. The full ACE model as well as three nested submodels (i.e. AE, CE and E) were fit to the data. The overall fit of these models was initially assessed with the chi-square goodness-of-fit statistic, with large (statistically significant) values leading to a rejection of the model. Nested models were then compared using the chi-square difference test where differences in chi-square values ($\chi^2\Delta$) were compared using as its degrees of freedom the difference in degrees of freedom for the two models. Finally, AIC ($\chi^2 - 2df$), a statistic that weighs model fit against model parsimony, was also used to select the best fitting model as indicated by the lowest AIC value.

RESULTS

Twenty-six (26/672; 3·8%) probands with AN syndrome were identified, including 13 (1·9%; 7 MZ, 6 DZ) twins with threshold and 13 (1·9%; 8 MZ, 5 DZ) twins with subthreshold AN. Table 1 presents probandwise concordance rates and model-fitting results. None of the DZ twins were concordant for AN, whereas 29% to 50% of MZ twins were concordant across diagnostic categories. A significant difference was observed between MZ and DZ twin concordance for AN syndrome, suggesting genetic effects.

The AE model provided the best fit to the data as indicated by its non-significant chi-square goodness-of-fit statistic, its non-significant chi-square difference from the ACE model, and its low AIC value. Parameter estimates from this model indicate that genetic and non-shared environmental factors accounted for 76% and 24% of the variance in AN syndrome, respectively.

Table 1. *Probandwise concordance rates* (N = 26)

	Probandwise concordance			
Anorexia nervosa	MZ	DZ	χ^2 (df = 1)	*P*
Threshold	0·29 (2/7)	0·00 (0/6)	—	—
Subthreshold	0·50 (4/8)	0·00 (0/5)	—	—
Syndrome	0·40 (6/15)	0·00 (0/11)	6·13	0·005

Table 2. *Model-fitting for AN syndrome*

Model	A	C	E	χ^2(df)	*P*	AIC
ACE	0·74 (0·00–0·94)	0 (0·00–0·65)	0·27 (0·06–0·67)	5·72 (2)	0·06	1·72
AE	**0·76 (0·35–0·95)**	**—**	**0·24 (0·05–0·65)**	**7·52 (4)**	**0·11[NS]**	**−0·48**
CE	—	0·52 (0·14–0·79)	0·48 (0·21–0·86)	11·61 (4)	0·02	3·61
E	—	—	0·99 (0·99–0·99)	18·69 (5)	0·002	8·69

A, Additive genetic effects; C, shared environmental effects; E, non-shared environmental effects. Standardized parameter estimates are provided in the 'A', 'C' and 'E' columns; 95% confidence intervals are noted in parentheses. The best fitting model is noted in bold type. It should be noted that the heritability estimate (0·75) obtained in a separate analysis (data not shown) that excluded the DZ twin pairs was almost identical to that in the best fitting model noted above, suggesting that the DZ twin concordance of 0·00 did not significantly affect results.

[NS]The chi-square difference ($\chi^2\Delta = 1{\cdot}8$, df = 2) between the ACE and AE models was non-significant ($P > 0{\cdot}05$).

DISCUSSION

The present investigation represents the first replication of genetic effects in a population-based twin study of AN syndromes. Additive genetic effects accounted for approximately 74% of the variance in broadly defined AN, with non-shared environmental influences accounting for the remaining variance. Notably, the 95% confidence intervals for these estimates were large, indicating that they are relatively imprecise. Nonetheless, the range of estimates are relatively similar to those obtained by clinical studies of AN (Holland *et al*. 1984, 1988) as well as the only other population-based twin study of the disorder to date (Wade *et al*. 2000). Taken together, results suggest significant genetic and non-shared environmental influence on anorexic pathology and that findings from patient-based samples are generalizable to individuals in the general population.

Several limitations should be noted. First, relatively small sample sizes prohibited analyses within individual diagnoses and likely limited our ability to detect shared environmental effects (Martin *et al*. 1978). Secondly, the disorder's low prevalence required the use of expanded phenotypes in analyses. Although this may have affected results, the likely effect would be to lower heritabilities below those obtained in studies with more homogeneous phenotypes, a result that is inconsistent with our relatively high heritability estimates.

Finally, the MTFS twins have not yet passed through the period of risk for eating pathology onset. Consequently, some 'discordant' cases may later prove to be 'concordant', potentially affecting heritability estimates. However, the relative proportion of MZ *versus* DZ concordant pairs may not change from late adolescence into adulthood. Similarities between our results and those of other studies using adult twins support this prediction. Notably, studying older twins who have passed through the risk period introduces retrospective recall biases that may also affect results. Thus, the optimal strategy for examining these effects is a longitudinal study where heritability can be examined cross-sectionally as well as across time. The MTFS represents such a study, as the twins will be followed for at least 9 years following baseline. This longitudinal assessment will enable us to

examine changes in disorder prevalence as well as developmental differences in genetic and environmental effects. Given findings of significant age differences in genetic influences on eating attitudes and behaviours across early to late adolescence (Klump *et al*. 2000), it will be essential to examine age-related changes in gene effects for AN.

This study was supported by grants from the National Institute on Drug Abuse (DA 05147) and the National Institute of Alcohol Abuse and Alcoholism (AA 09367).

REFERENCES

Akaike, H. (1987). Factor analysis and the AIC. *Psychometrika* **52**, 317–332.

Garner, D. M., Olmsted, M. P. & Polivy, J. (1983). Development and validation of a multidimensional eating disorder inventory for anorexia nervosa and bulimia. *International Journal of Eating Disorders* **2**, 15–34.

Holland, A. J., Hall, A., Murray, R., Russell, G. F. M. & Crisp, A. H. (1984). Anorexia nervosa: a study of 34 twin pairs. *British Journal of Psychiatry* **145**, 414–419.

Holland, A. J., Sicotte, N. & Treasure, J. (1988). Anorexia nervosa: evidence for a genetic basis. *Journal of Psychosomatic Research* **32**, 561–571.

Iacono, W. G., Carlson, S. R., Taylor, J., Elkins, I. J. & McGue, M. (1999). Behavioral disinhibition and the development of substance use disorders: findings from the Minnesota Twin Family Study. *Development and Psychopathology* **11**, 869–900.

Klump, K. L., McGue, M. & Iacono, W. G. (2000). Age differences in genetic and environmental influences on eating attitudes and behaviors in preadolescent and adolescent female twins. *Journal of Abnormal Psychology* **109**, 239–251.

Lilenfeld, L. R., Kaye, W. H., Greeno, C. G., Merikangas, K. R., Plotnicov, K., Pollice, C., Rao, R., Strober, M., Bulik, C. M. & Nagy, L. (1998). A controlled family study of anorexia nervosa and bulimia nervosa: psychiatric disorders in first-degree relatives and effects of proband comorbidity. *Archives of General Psychiatry* **55**, 603–610.

McGue, M. (1992). When assessing twin concordance, use the probandwise not the pairwise rate. *Schizophrenia Bulletin* **18**, 171–176.

Martin, N. G., Eaves, L. J., Kearsey, M. J. & Davies, P. (1978). The power of the classical twin study. *Heredity* **40**, 97–116.

Neale, M. C. (1995). *Statistical Modeling*, *3rd edn*. Department of Psychiatry: Box 710 MCV, Richmond, VA 23298.

Spitzer, R. L., Williams, J. B. W. & Gibbon, M. (1987). *Structured Clinical Interview for DSM-III-R* (*SCID*). New York State Psychiatric Institute, Biometrics Research: New York.

Strober, M., Freeman, R., Lampert, C., Diamond, J. & Kaye, W. (2000). A controlled family study of anorexia nervosa and bulimia nervosa: evidence of shared liability and transmission of partial syndromes. *American Journal of Psychiatry* **157**, 393–401.

Treasure, J. & Holland, A. (1990). Genetic vulnerability to eating disorders: Evidence from twin and family studies. In *Child and Youth Psychiatry: European Perspectives* (ed. H. Remschmidt, M. Schmidt and N. Y. Lewiston), Hogrefe & Huber: Lewiston, NY.

Wade, T. D., Bulik, C. M., Neale, M. & Kendler, K. S. (2000). Anorexia nervosa and major depression: an examination of shared genetic and environmental risk factors. *American Journal of Psychiatry* **157**, 469–471.

Walters, E. E. & Kendler, K. S. (1995). Anorexia nervosa and anorexic-like syndromes in a population-based female twin sample. *American Journal of Psychiatry* **152**, 64–71.