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Monozygotic twin pairs discordant for lifetime anorexia nervosa: An exploratory investigation

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Abstract

Although there is an increasing understanding of the impact of genetic factors on the development of anorexia nervosa (AN), clear identification of environmental risk factors remains unclear. Using monozygotic twins discordant for a disorder can be a useful tool for identifying such environmental risk factors. Differences between nine pairs of female monozygotic twins in the Australian Twin Registry who were discordant for lifetime AN were investigated. Twins were compared on self-report measures, including measures of current and lifetime psychopathology, temperament and coping, and parental bonding. None of the twins currently met the weight criterion for AN, indicating that current psychopathology would be unlikely to affect results. The twin affected by past AN reported a higher birth weight but a lower current body mass index than their co-twin; the affected twin tended to be more anxious than their co-twin. It may be useful for larger studies to further explore differences between twins discordant for AN in the areas of novelty seeking, and ways of coping, especially with respect to seeking social support.

Eating disorders are far from benign: out of 27 mental disorder categories examined, one of the highest risks of premature death, from both natural and unnatural causes, is associated with eating disorders (Harris & Barraclough, 1998). Most of this mortality can be attributed to anorexia nervosa (AN), given that women with this disease are up to four times more likely to die than other women of the same age (Crisp, Callender, Halek, & Hsu, 1992). Therefore investigation and identification of the risk factors for the development of AN are an area of high priority.

Genetic risk factors for the development of AN have been indicated in two populations, the Danish twin registry (Kortegaard, Hoerder, Joergensen, Gillberg, & Kyvik, 2001) and the Virginia twin registry (Wade, Bulik, Neale, & Kendler, 2000; Walters & Kendler, 1995), with estimates for heritability of 48% and 58% respectively. Equally, the nonshared environment (environmental factors that are unique to each sibling growing up in the same family) has also been shown to contribute substantially to the development of AN (Kortegaard et al., 2001; Wade et al., 2000). In other words, environmental factors that are unique to family members are more important in influencing the development of behaviour than environments shared by family members. Nonshared environment has been described as consisting of two types (Turkheimer & Waldron, 2000). The first is *effective* nonshared environment, where the same event can be experienced uniquely by each family member, depending on a number of factors such as age and temperament, thus producing differential outcomes. The second is *objective* nonshared environment, where an actual experience or event is not shared by siblings. Finally, the contribution of the shared environment to AN, an event that occurs to both siblings and is experienced in the same way by them, cannot be ruled out. However, the influence is likely to be comparatively smaller than either

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genetic influences or the nonshared environment (Wade et al., 2000).

These findings are consistent with the body of behaviour genetics research from the last couple of decades. The basic findings for heritability of major psychiatric disorders and psychopathology have become well established and replicated over the last few decades of research (Paykel, 2002; Rutter & Silberg, 2002), and contribution of the nonshared environment to these psychopathologies has been found to be considerable (Plomin, Chipuer, & Neiderhiser, 1994). Complex traits are understood to be influenced by many genes and many specific environmental factors, and hence genetic factors are seen to operate in a probabilistic fashion, like risk factors rather than predetermined programming (Plomin, 2000). In terms of prevention and treatment of eating disorders, identification of the types of specific environments that may increase the likelihood of expression of genetic vulnerability is of particular interest (Bulik, Sullivan, Wade, & Kendler, 2000; Fairburn, Cowen, & Harrison, 1999; Paykel, 2002; Rutter, Pickles, Murray, & Eaves, 2001; Rutter & Silberg, 2002).

While twin studies are often identified as tools for identifying heritability of disorders, they are also powerful tools for identifying nonshared environmental factors that influence the development of eating disorders (Klump, Wonderlich, Lehoux, Lilenfeld, & Bulik, 2002). In particular, the discordant monozygotic (MZ) twin design has been used to some benefit in examining environmental risk factors. This design is based on the understanding that any differences between MZ twins, who for most intents and purposes share all of their genes, provides strong evidence for the role of environmental influences (Plomin, DeFries, McClearn, & Rutter, 1994, pp. 171–172). These environmental influences include a variety of prenatal events (Martin, Boomsma, & Machin, 1997). Monozygotic twins, although carrying identical DNA sequences, do not necessarily experience the same intrauterine environment, and therefore may have different degrees of methylation of autosomal genes, which might contribute to different complex diseases developing in identical twins (Petronis, 2001). Estimates of nonshared environmental influences also include measurement error because these effects can also make co-twins differ.

The discordant MZ design has been used to investigate environmental influences on bulimia nervosa (BN) in four studies. An examination of 30 pairs of MZ twins discordant for broadly defined BN indicated that affected twins had more anxious traits (as reported by both twins and their mothers), including lower mastery, optimism, and self-esteem, as well as greater anxiety, fearfulness, and anxiety disorder symptoms (Bulik, Wade, & Kendler, 2001). In addition, affected twins recalled greater discord in the family. A second study investigated differences between nine pairs of female MZ twins in the Australian Twin Registry who were discordant for lifetime BN (Wade, Treloar, & Martin, 2001). No twins had current BN and there were no differences in weight or eating status. The twins were compared on self-report measures, including a measure of parental bonding, five measures of temperament, and six early childhood conditions. The twin affected by past BN reported significantly lower self-esteem, and less warmth but more overprotection from their mother when growing up. A third study found that the risk for BN was significantly associated with childhood sexual abuse in twins discordant for such abuse (Kendler et al., 2000), even after controlling for the potential confounding effects of family background factors and parental psychopathology. Finally, intrauterine growth discordance was found to predict BN but not any other disorders, including AN, depression and anxiety disorders (Foley, Neale, & Kendler, 2001).

To date, no studies have used the discordant MZ design for twins discordant for AN, a disorder that is much more difficult to study due to its extremely low prevalence rate. In the current study we therefore seek to conduct an exploratory investigation of risk factors for AN using nine pairs of MZ twins discordant for lifetime AN. We examine the differences between affected and unaffected twins for reports of weight variables, current psychopathology, temperament and coping styles, and family functioning when growing up. At the time of assessment none of our sample met weight criteria for AN, thereby avoiding the effect of being underweight on reporting.

Method

Participants

The data are from a longitudinal study of 1,682 women in the volunteer Australian Twin Registry who were screened with a self-report Health and Lifestyle survey (1988–1989). At the time of screening, these women were between the ages of 30 and 45 years ($M = 36.5$, $SD = 4.7$). These women were further interviewed over the telephone in 1992–1993 with a general semistructured psychiatric interview that included information about lifetime AN and BN. Nine MZ twin pairs were found to be discordant for lifetime history of AN, with cessation of menses not being a necessary requirement for diagnosis. The mean age of these 18 women at the

time of the questionnaire survey was 32.6 years ($SD = 2.6$) and at telephone interview was 36.7 years ($SD = 2.6$), ranging from 33 to 40 years. The lowest weight was reached at a mean age of 19.0 years ($SD = 5.2$), ranging from 12 to 28 years. The body mass index (BMI) at the time of questionnaire for women with a past history of AN ranged from 18.8 to 27.9, indicating that none met the current diagnostic weight criterion for AN. Oral informed consent was obtained before proceeding with the telephone interview.

Instruments

The psychiatric interview utilised at the second wave of data collection was the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), modified for use in Australia (Bucholz et al., 1994). It comprises items previously validated by other research interviews, such as the Composite International Diagnostic Interview (World Health Organization [WHO], 1993). A subset of these questions assessed lifetime presence of *Diagnostic and statistical manual of mental disorders* (3rd ed., revised; *DSM-III-R*) AN, BN, and anxiety disorders, including social phobia, panic disorder and agoraphobia.

Measures of current psychopathology, temperament, coping, family functioning and birth weight were collected by mailed questionnaire at the time of the first wave of data collection. An abbreviated version of the Symptom Checklist (SCL; Derogatis, 1975) was used to collect measures of current psychopathology. Temperament measures included the Rosenberg Self-Esteem scale (Rosenberg, 1965), the Eysenck Personality Questionnaire (EPQ; Eysenck, Eysenck, & Barrett, 1985), the Tridimensional Personality Questionnaire (TPQ; Cloninger, Przybeck, & Svrakic, 1991) and the Ways of Coping Questionnaire (WOC; Lazarus, 1993). Warmth (or care) and overprotection from parents in the first 16 years of life was measured with the 25-item Parental Bonding Inventory (PBI; Parker, Tupling, & Brown, 1979). These measures have been previously described (Treloar, McDonald, & Martin, 1999).

Analyses

Paired *t* tests were used for all measures. Given the clear directional hypotheses from previous research literature, one-tailed significance was used for all *t* tests with the exception of the birth weight variable. Because this represents an exploratory investigation, we have chosen not to correct for multiple comparisons. All analyses were conducted using SPSS for Unix, Release 6.1.

Results

Assessment of other eating difficulties

None of the twins met lifetime criteria for BN. Five of the twins unaffected with AN did indicate some lifetime eating disturbance: two had experienced a great degree of concern about their weight, two had experienced binge-eating, and one had lost weight to a BMI of < 17.5 but reported no accompanying symptoms of AN.

Differences between the twins

The results of the paired comparisons of the continuous variables are presented in Table I. The twin with a lifetime history of AN had a significantly higher birth weight and a significantly lower current BMI than their co-twin. The mean BMI values for both the affected and unaffected twins were in the normal range. Affected twins had higher levels of current psychopathology than their co-twins but these differences were not significant.

Differences in current anxiety levels approached significance. Diagnoses of anxiety disorders were subsequently examined for the nine pairs of twins. No unaffected twins met criteria for anxiety disorders. Two twins with AN met criteria for an anxiety disorder: one had lifetime panic disorder and the other had lifetime panic disorder with agoraphobia as well as social phobia. The age of onset of the panic disorder indicated that onset occurred after the development of AN for those twins. The social phobia was reported to develop at age 5. A further two affected twins experienced agoraphobic anxiety that was not associated with avoidance behaviour; in one case this anxiety occurred before the development of the AN.

Discussion

The purpose of this study was to explore possible environmental risk factors for AN using the discordant MZ co-twin control design. Although significant differences between the nine pairs of twins discordant for AN were few—in contrast to the findings with twins discordant for BN—some interesting findings did emerge. The twin with the lifetime history of AN had a significantly higher birth weight than the unaffected co-twin. To date, no studies have found birth weight to be a risk factor for AN (Foley, Thacker, Aggen, Neale, & Kendler, 2001), but a very preterm birth is associated with AN in an inpatient sample (Cnattingius, Hultman, Dhal, & Sparen, 1999). A lower gestational age is also significantly associated with increased risk for AN in twins as are prenatal complications (Foley, Thacker, et al., 2001). Given the research implicating prenatal

Table I Comparison of nine pairs of monozygotic twins discordant for lifetime anorexia nervosa

Variable	Affected *M* (*SD*)	Unaffected *M* (*SD*)	*t df* = 8	*p*	Effect size (*d*)
Weight					
Birth weight (g)	2450.67 (460)	2214.44 (489)	2.87	.02*[a]	0.48
BMI – interview	21.25 (2.91)	23.70 (4.50)	−2.72	.01*	0.54
Psychopathology (current)					
SCL-90-somatisation	1.53 (0.81)	1.31 (0.57)	0.66	.26	0.38
SCL-90-depression	1.58 (0.66)	1.38 (0.16)	0.90	.20	1.25
SCL-90-anxiety	1.50 (0.64)	1.17 (0.22)	1.60	.07	1.50
SCL-90-phobic anxiety	1.40 (0.78)	1.09 (0.18)	1.14	.14	1.72
Temperament					
Self esteem	2.93 (0.57)	3.02 (0.29)	−0.51	.31	0.31
EPQ extroversion	1.81 (0.64)	1.83 (0.59)	0.07	.47	0.03
EPQ neuroticism	2.06 (0.67)	2.00 (0.59)	0.46	.33	0.11
EPQ impulsiveness	1.73 (0.52)	1.67 (0.32)	0.78	.23	0.19
TPQ novelty seeking	1.67 (0.23)	1.92 (0.41)	−1.59	.08	0.61
TPQ reward dependence	2.26 (0.40)	2.14 (0.35)	0.42	.34	0.34
TPQ harm avoidance	2.09 (0.60)	2.17 (0.34)	−0.79	.23	0.24
WOC – seeking social support	2.31 (0.51)	2.58 (0.50)	−1.19	.13	0.54
WOC – problem-focussed	2.33 (0.63)	2.27 (0.42)	0.31	.38	0.14
WOC – denial	2.54 (0.78)	2.26 (0.37)	1.08	.16	0.76
Family functioning – up to age 16					
PBI mother care	3.30 (0.70)	3.26 (0.52)	0.13	.45	0.08
PBI mother overprotection	2.07 (0.82)	2.17 (0.69)	−0.51	.31	0.15
PBI father care	3.19 (0.65)	3.30 (0.56)	−0.47	.32	0.20
PBI father overprotection	1.77 (0.73)	2.06 (0.61)	−1.32	.11	0.48

Note. BMI = body mass index; SCL = Symptom Checklist; EPQ = Eysenck Personality Questionnaire; TPQ = Tri-dimensional Personality Questionnaire; WOC = Ways of Coping Questionnaire; PBI = Parental Bonding Inventory.
[†]0.2 – 0.49 = small effect size; 0.5 – 0.79 = medium effect size; 0.8 = large effect size.
[a]Two-tailed probability (all other tests are one-tailed).
*$p < .05$.

complications it might be expected that a lower birth weight would be associated with the development of AN. However, we know that being overweight as children may be a salient experience for women who develop an eating disorder (Fabian & Thompson, 1989). It may be that if this comparative difference in weight is translated to childhood, this could act as a trigger experience for the heavier twin. This speculation is somewhat supported by the finding that greater adolescent co-socialisation predicts twin concordance for BN (Bulik, Sullivan, & Kendler, 1998), that is, more socialising together in adolescence is associated with a greater likelihood that both twins in the pair will have BN. Although greater co-socialisation may predict BN, this may actually produce discordance for AN when coupled with differential body weight in one's identical twin. For the twin with the larger body size or heavier weight, comparison with a thinner identical sibling in a variety of social situations may promote greater body dissatisfaction, especially during adolescence when issues about appearance tend to be more critical.

Those twins affected by AN in the past continued to maintain a significantly lower body weight than their unaffected co-twin, while no longer meeting current weight criteria for AN. This is despite the course of AN being most severe between 3 and 19 years earlier, as indicated by the time of the lowest BMI being reached. This suggests that a lifetime history of AN continues to have long-term consequences. This finding is congruent with follow-up research over a 20-year period that finds that only 30 – 50% of women with AN have a good outcome (Lowe et al., 2001; Ratnasuriya, Eisler, Szmukler, & Russell, 1991).

Consistent with previous literature (Bulik, Sullivan, Fear, & Joyce, 1997), we find that the twin affected by a lifetime history of AN experienced a tendency to higher levels of anxiety than their co-twin. The relationship of this anxiety to AN is uncertain. We found that panic disorder occurred after the development of AN but that social phobia preceded it, as have others (Bulik et al., 1997). Agoraphobia occurred both before and after the appearance of the eating disorder. This may indicate that there are common risk factors between anxiety disorders and AN, such as the temperament trait of low novelty seeking (Bulik et al., 1997).

The present study can be viewed as only an exploratory investigation given only nine MZ pairs of twins discordant for AN. Given that there are few differences between twins who are discordant for AN

compared to the same number of twins discordant for BN (Wade et al., 2001), our ability to distinguish clearly between the siblings in each pair may have been obscured by the fact that the majority of unaffected twins had experienced disturbed eating. The findings must also be interpreted in the context of possible retrospective recall bias and the difficulty of distinguishing risk factors from sequelae in cross-sectional, retrospectively reported co-twin control studies. Future studies, ideally prospective, are required in order to more specifically identify the life events that may differ between discordant twins and the role of these in increasing the substantial genetic vulnerability to developing AN. Also, it may be useful for larger studies to further explore differences between twins discordant for AN in the areas of anxiety (especially phobic anxiety), novelty seeking, and ways of coping, especially with respect to seeking social support.

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