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Puberty moderates genetic influences on disordered eating

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ABSTRACT

Background. Previous research suggests that genetic influences on disordered eating may be greater in pubertal than pre-pubertal girls. Although these findings are consistent with pubertal activation of genetic influences on disordered eating, earlier studies were unable to directly test this hypothesis. The purpose of the present study therefore was to directly examine this possibility by investigating whether pubertal development moderates genetic influences on disordered eating.

Method. Participants were 510 female adolescent twins from the Minnesota Twin Family Study. Disordered eating was measured with the Total Score of the Minnesota Eating Behavior Survey, while pubertal status was assessed with the Pubertal Development Scale.

Results. Consistent with our hypothesis, model-fitting indicated significant increases in genetic influence on disordered eating with advancing pubertal development.

Conclusions. These findings suggest that puberty influences the expression of genes for disordered eating.

INTRODUCTION

Anorexia nervosa (AN) and bulimia nervosa (BN) often begin during puberty or shortly thereafter (APA, 2000). Significant increases in disordered eating have been found across puberty for several types of symptoms, including weight preoccupation, body dissatisfaction, and binge-eating (Bulik, 2002; Klump *et al.* 2003). Studies suggest linear increases in disordered eating across puberty (Killen *et al.* 1992; Graber *et al.* 1994; Bulik, 2002), although some indicate nonlinear changes with increases through mid-puberty when symptom levels plateau (Killen *et al.* 1992; Hayward & Sanborn, 2002).

Theories accounting for heightened pubertal risk have focused on the psychosocial impact of physical changes that occur during puberty (Bulik, 2002), most notably increases in body fat in girls (Graber *et al.* 1994). These theories postulate that increased adiposity leads to negative affect and body dissatisfaction which, in turn, increase risk for eating (Graber *et al.* 1994) and related disorders (e.g. depression; Angold *et al.* 1999; Hayward *et al.* 1997).

Importantly, recent work has highlighted the role of biological or genetic mediation of these pubertal effects. In a series of developmental twin studies from the Minnesota Twin Family Study (MTFS) (Klump *et al.* 2000, 2003), we found that the heritability of disordered eating symptoms increases across puberty. Using a sample of pre-adolescent twins, genetic influences on disordered eating symptoms were minimal (i.e. 0%) in pre-pubertal twins, while genetic effects were substantial (>50%) in twins who had begun puberty (Klump *et al.* 2003). A second twin study, however, did not find

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significant effects of puberty on the heritability of disordered eating (Rowe *et al*. 2002), though findings were limited by the use of menarche as the only indicator of pubertal development. Given that menarche is the last stage of puberty, several twins who had begun puberty (and thus, had likely begun exhibiting genetic effects) were categorized as pre-pubertal, thereby confounding groups and possibly leading to non-significant differences in genetic effects.

Given discrepant results, the aim of the present study was to extend previous findings by directly examining whether puberty moderates genetic influences on disordered eating using a follow-up assessment of the MTFS twins. In our initial analyses, the majority of twins were 11 years old (age range 10–13 years) and pre-pubertal. The current study examines these same twins three years later when most have begun puberty (age range = 13–16 years; mean = 14·78; S.D. = 0·52) to determine whether increases in heritability across puberty remain despite within-twin shifts in pubertal status (i.e. from early to mid-puberty, or mid-puberty to post-puberty). Moreover, we extend previous analyses by using recently developed twin moderation models (Purcell, 2002) to directly examine whether there are linear and non-linear changes in genetic effects across puberty. This last benefit is particularly important given data showing both types of increases in disordered eating across puberty (see above). Testing each of these effects will allow us to identify patterns of genetic influence across development that may inform molecular genetic studies of these symptoms.

METHOD

Participants

The sample comprises 510 adolescent female twins [326 MZ twins (163 pairs), 184 DZ twins (92 pairs)] drawn from the second wave of data collection (see above) from the prospective MTFS. Recruitment procedures and study methodology for the MTFS have been described previously (Iacono *et al*. 1999). Twin zygosity was established using twin and research assistant ratings of within-pair physical similarity and an algorithm diagnosis calculated from ponderal index, cephalic index, and fingerprint ridge count (Iacono *et al*. 1999). Disagreements among these measures were resolved through serological examination of 12 blood group antigens and protein polymorphisms.

Measures

Disordered eating

Similar to our previous study (Klump *et al*. 2003), overall levels of disordered eating were assessed using the Total Score from the Minnesota Eating Behavior Survey (MEBS; Klump *et al*. 2000; von Ranson *et al*. 2005). The Minnesota Eating Behavior Survey [MEBS; previously known as the Minnesota Eating Disorder Inventory (M-EDI)] was adapted and reproduced by special permission of Psychological Assessment Resources, Inc. from the Eating Disorder Inventory (collectively, EDI and EDI-2) by D. Garner, M. Olmstead and J. Polivy. (© 1983 by Psychological Assessment Resources, Inc., 16204 North Florida Avenue, Lutz, Florida 33549, USA. Further reproduction of the MEBS is prohibited without prior permission from Psychological Assessment Resources, Inc.)

The MEBS Total Score includes items that assess body dissatisfaction, binge eating, weight preoccupation, and the use of inappropriate compensatory behaviors. Previous studies have supported the reliability ($\alpha = 0{\cdot}87$; von Ranson *et al*. 2005) and validity of this scale (Klump *et al*. 2000; von Ranson *et al*. 2005), including showing that scores differentiate women with and without eating disorders.

Puberty

The Pubertal Development Scale (PDS; Petersen *et al*. 1988) was used to assess pubertal development in the areas of height spurts, body hair growth, skin changes, breast development, and initiation of menses. Subjects self-rated their development in these areas on a four-point scale: (1) development has not yet begun; (2) development has barely started; (3) development is definitely underway; and (4) development seems completed. Menstruation was rated dichotomously as absent (1) or present (4). Similar to previous research (Petersen *et al*. 1988), average scores (i.e. range 1–4) across all five items were used in analyses. Previous studies of the PDS psychometric properties have supported its reliability (median $\alpha = 0{\cdot}77$; Petersen *et al*. 1988) and validity, including showing high correlations ($r = 0{\cdot}61$–$0{\cdot}67$) with clinician

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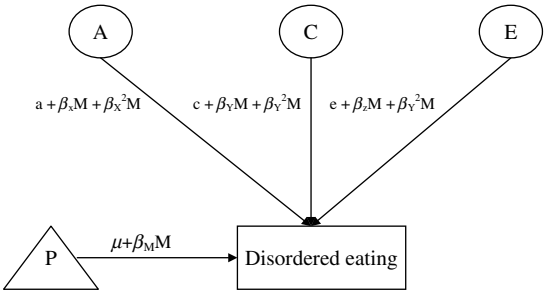

FIG. 1. Path diagram for the full moderation model for one twin only. (P, puberty; A, additive genetic effects; C, shared environmental effects; E, non-shared enviromental effects; M, Moderator; β_M, phenotypic regression coefficient; a, c, and e, paths or intercepts; β_X, β_Y, β_Z, linear moderators; β_X^2, β_Y^2, β_Z^2, quadratic moderators.)

ratings of pubertal development (Petersen *et al.* 1988).

Statistical analyses

Pubertal moderation of genetic and environmental influences on disordered eating was examined using nested gene-environment interaction models (Purcell, 2002). In all of these models, we examined additive genetic (A; genetic influences that add across genes), shared environmental (C; environmental influences that are shared by reared-together twins and are thus a source of behavioral similarity), and non-shared environmental (E; environmental influences that are not shared by reared-together twins and are thus a source of behavioral dissimilarity) influences. The full ACE model was examined in analyses rather than reduced models (e.g. AE) since previous analyses suggest significant shared environmental influences on disordered eating in girls during early puberty (Klump *et al.* 2003).

The interaction models estimate three sets of parameters that conjointly index the extent to which genetic and environmental influences on disordered eating differ significantly across levels of pubertal development (see Fig. 1). The first set of parameters contain the 'paths' or intercepts (i.e. a, c, and e) and estimate the degree of genetic and environmental influence on disordered eating at the lowest level of pubertal development (i.e. '0' in these modeling analyses, as PDS scores were floored with a minimum of 0 for ease of interpretation). The second set of parameters are the linear moderators (i.e. β_X, β_Y, β_Z) which assess the extent to which genetic and environmental influences on disordered eating increase or decrease linearly with pubertal development. The final set of parameters are the quadratic moderators (i.e. β_X^2, β_Y^2, β_Z^2) which assess the extent to which there are non-linear increases or decreases in genetic and environmental influences on disordered eating across puberty.

Following previous recommendations (Purcell, 2002) and research (e.g. Burt *et al.* 2006), we fit a series of nested interaction models to the observed data. The first model functioned as a baseline main effects model in which only the genetic, shared, and non-shared environmental path estimates or intercepts were computed. In the second and third models, we respectively added linear and then non-linear genetic, shared, and non-shared environmental moderators. These models could detect whether there were linear or non-linear shifts in the amount of genetic and environmental variance in disordered eating with advanced pubertal development.

The full model, containing all three sets of parameters (i.e. the paths, the linear, and the quadratic moderators), was used to assess the extent to which there were non-linear changes in genetic and environmental influences on disordered eating across pubertal development. This model was then compared to two separate nested models. The first nested model was the most restrictive and contained the paths but dropped the linear and quadratic moderators. This model thus constrained genetic and environmental influences to be constant across levels of pubertal development. The second nested model included the paths and the linear moderator effects, but dropped the quadratic moderators. This model was then compared to the full model to determine if there are linear, but not quadratic, increases or decreases in genetic and environmental influences on disordered eating scores across pubertal development. The two reduced models (i.e. no moderation model and linear moderation only model) were compared statistically to the full model by taking the difference in minus twice the log-likelihood (-2 ln L) between the full and reduced models, which is chi-squared distributed under the null hypothesis implied by the reduced model. Large (statistically significant) differences led to a rejection of the nested model in favor of the

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full model, as this suggests that dropping the parameters from the full model resulted in a significantly worse fit of the data.

Models were fit to the raw twin observations using the Mx statistical software (Neale, 1995). The raw data option in Mx treats missing data as missing at random (Little & Rubin, 1987), and thus the parameter estimates and fit indices are appropriately adjusted, and twin pairs are retained in analyses even if one member of the pair is missing MEBS data. We log-transformed the MEBS and PBS data prior to model-fitting, as increases or decreases in variance with values of the moderator can bias model-fitting results. We also standardized the MEBS scores to enhance visual comparisons of changes in genetic and environmental influences across pubertal development. Following previous recommendations (Purcell, 2002), we report the unstandardized parameter estimates in tables and figures, as these estimates more accurately depict absolute changes in genetic and environmental influences than standardized estimates which represent these changes as proportions of the total variance.

RESULTS

The majority of twins were in mid-to-late puberty (mean = 3·33, S.D. = 0·43), although the range of MEBS (range = 0–23; mean = 5·89, S.D. = 5·67) and averaged PDS (range = 1·60–4·00) scores indicate considerable variability in disordered eating and pubertal development. Log-transformed MEBS scores were significantly lower [$t(508) = -2{\cdot}49$, $p = 0{\cdot}01$] in twins who were in the lower (i.e. PDS average score $\leqslant 2{\cdot}6$) (mean = 0·58, S.D. = 0·30) *versus* those in the middle-to upper end of the PDS distribution (i.e. PDS average score $> 2{\cdot}6$; mean = 0·78, S.D. = 0·33). However, MEBS score variances did not differ significantly between these group [Levene's Test of Equality of Variances: $F(1, 508) = 1{\cdot}35$, $p = 0{\cdot}25$], indicating that differential variability in disordered eating across puberty cannot account for differences in etiologic effects observed in this study (see below).

The Pearson correlation between PDS scores and disordered eating ($r = 0{\cdot}10$, $p = 0{\cdot}007$) suggested a significant positive association between pubertal development and overall eating pathology. Although this relationship was modest, it does not preclude the presence of moderator effects, as significant genetic or environmental moderators would be expected to attenuate phenotypic associations.

Results from the model-fitting analyses are presented in Table 1 and Fig. 2. Significant differences in -2lnL values between the full and most restricted nested model (i.e. the model that dropped all moderators) indicate that the linear and quadratic moderators cannot both be dropped from the model without a significant worsening of fit. These findings suggest that puberty does moderate genetic and environmental influences on disordered eating. However, the non-significant p value for the change in -2lnL values (i.e. $p > 0{\cdot}05$) between the full model and the model dropping the quadratic moderator indicates that only the linear moderator effects are important for disordered eating, and that the model that includes the linear moderators, but not the quadratic moderators, is the best-fitting for the puberty/disordered eating data.

Fig. 2 graphs the unstandardized parameter estimates (see Purcell, 2002, for equations for these estimates) for this best-fitting model, and shows that the influence of genes increases dramatically with advancing pubertal development. Using data in Table 1, we calculated the phenotypic proportions of disordered eating accounted for by genes at the two extreme levels of pubertal development (i.e. 0 and 1·11 on the log-transformed scale constructed after flooring PDS scores to have a minimum of 0; see Methods above) to determine the magnitude of increases in genetic effects across the pubertal period. It is important to note that these log-transformed values correspond to puberty levels of 2·6 (early puberty) and 4·0 (post-puberty) on a non-log-transformed, non-floored scale. The heritability of disordered eating was found to increase from 0% to 44% across these pubertal stages. The increase in genetic effects appeared to occur at a log-transformed score of approximately 4·0, which corresponds to an averaged PDS score of 3·0 (middle puberty). Taken together, these findings confirm our hypothesis that genetic effects on disordered eating are moderated by pubertal development.

In contrast to genetic effects, the influence of shared environment decreases dramatically across puberty from accounting for 99% of the

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Table 1. *Model fit indices and unstandardized parameter estimates*

Model	Paths			Linear			Quadratic			Model fit indices	
	a	c	e	β_X	β_Y	β_Z	$\beta_X{}^2$	$\beta_Y{}^2$	$\beta_Z{}^2$	−2lnL (df)	$-2\ln L_\Delta$ (df)
Full	−0·23 (−0·90, 0·77)	1·10 (0·62, 1·53)	0·03 (−0·23,0·20)	1·55 (−0·68, 2·0)	−0·70 (−2·99, 1·23)	1·73 (0·92, 2·00)	−0·42 (−0·80, 0·80)	−0·60 (−2·0, 2·0)	−1·17 (−1·72, 0·06)	1371·52 (499)	—
Drop All Mod.	−0·68 (−0·82, −0·26)	0·23 (−0·64, 0·64)	−0·69 (−0·78, −0·63)	—	—	—	—	—	—	1386·23 (505)	14·71* (6)
Drop-Quad Mod. Only	**0·11 (−0·61, 0·97)**	**1·23 (0·74, 1·6)**	**0·03 (0·01, 0·72)**	**0·75 (−0·41, 1·6)**	**−1·30 (−1·9, 0·67)**	**0·92 (−0·08, 1·1)**	—	—	—	**1378·53 (502)**	**7·01 (3)**

Each nested model is compared to the full model when calculating the change in −2lnL and degrees of freedom. The best-fitting model is noted by bold text.
A, Main effects of genes; C, main effect of shared environment; E, main effect of non-shared environment; β_X, linear interaction between genes and puberty; β_Y, linear interaction between shared environment and puberty; β_Z, linear interaction between genes and non-shared environment; $\beta_X{}^2$, non-linear interaction between genes and puberty; $\beta_Y{}^2$, non-linear interaction between shared environment and puberty; $\beta_Z{}^2$, non-linear interaction between non-shared environment and puberty; Full, model with paths, linear moderators, and quadratic moderators; Drop All Mod., model with paths only, Drop Quad Mod. Only, model with paths and linear moderators only.
* $p = 0{\cdot}02$.

FIG. 2. Contributions of genes, shared environment, and non-shared environment to disordered eating across pubertal development. Using data in Table 1, the authors calculated the phenotypic proportion of disordered eating accounted for by genes at the two extreme levels of pubertal development (i.e. 0 and 1·11 on the log-transformed scale constructed after flooring PDS scores to have a minimum of 0; see Methods) to determine the magnitude of increases in genetic effects across the pubertal period. It is important to note that these log-transformed values correspond to puberty levels of 2·6 (early puberty) and 4·0 (post puberty) on a non-log-transformed, non-floored scale. The heritability of disordered eating was found to increase from 0% to 44% across these pubertal stages. ——, Additive genetic effects; – – –, shared environment; - - -, non-shared environment.

variance in early puberty to 2% in post puberty. Non-shared environmental influences increase and then plateau in middle-to-late puberty (i.e. raw averaged PDS score = 3·4). Nonetheless, these types of influences account for similar amounts of variance as genetic effects in early (1%) and post (54%) puberty.

DISCUSSION

This is the first study to directly examine pubertal moderation of genetic effects on disordered eating. Findings replicate and extend our previous analyses (Klump *et al.* 2003) by suggesting that genetic effects on disordered eating become prominent during puberty and increase linearly in importance across pubertal development. By contrast, shared environmental influences decrease across the pubertal period. These results indicate that puberty influences disordered eating primarily via genetic and non-shared environmental factors, rather than the shared environmental influences often theorized to be primary (e.g. Marsden & Holmbeck, 2002).

It will be important for future studies to identify the processes underlying these moderating effects. Changes in several psychological

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(e.g. mood), psychosocial (e.g. peer groups), and physical (e.g. bodyweight) characteristics coincide with pubertal changes in girls and are associated with increases in disordered eating symptoms (Bulik, 2002). Our findings show that puberty moderates *genetic influences* on disordered eating – not increases in disordered eating incidence. Thus, if the factors described above account for the moderating effects of puberty, they must operate to increase genetic, and decrease environmental, influences. Notably, changes in mood could influence the heritability of disordered eating through changes in serotonin functioning or other neurobiological systems that are known to be involved in mood regulation (van der Veen *et al.* 2007).

It is more difficult to conceptualize how changes in psychosocial factors such as peer interactions might influence the heritability of disordered eating. Although this may occur through active gene-environment correlations (i.e. girls with genetic predispositions for eating pathology select peers who are more weight-concerned, thereby enhancing pre-existing genetic vulnerabilities and increasing heritability) (Scarr & McCartney, 1983), this process would need to occur rather rapidly during puberty in order for it to account for the effects observed in this study. Thus, these processes are less likely candidates in the search for factors underlying the pubertal moderation of genetic effects on puberty.

More likely candidates are ovarian hormones that are activated during puberty in girls. Although other biological systems are also involved in puberty (e.g. stress hormones and the hypothalamic-pituitary axis), ovarian hormones drive pubertal changes in girls. Thus, ovarian hormones are probable contributors to sex differences in eating disorder prevalence (APA, 2000) and the moderating effects of puberty observed in this study.

Importantly, ovarian hormones are known to affect food intake and body weight, characteristics that are disrupted in eating disorders (see Wade, 1972) and are known to change with pubertal development. For example, animal studies show decreased dietary intake during peak estrogen levels in female rats (Blaustein & Wade, 1977) as well as weight loss in ovariectomized female rats exogenously treated with estradiol (Varma *et al.* 1999). Progesterone has the opposite effects of estrogen, with increased progesterone levels being associated with increased dietary intake and weight gain (van der Schoot *et al.* 1991; Ganesan, 1994).

Studies in humans have confirmed these findings. Decreased levels of estrogen, and increased levels of progesterone, are associated with increased food intake and body weight in adult women (e.g. Wade, 1972; Buffenstein *et al.* 1995). Importantly, these findings appear to extend to disordered eating patterns as well. Estrogen levels are associated with disordered eating during the follicular phase of the menstrual cycle (Klump *et al.* 2006), and natural fluctuations in estrogen and progesterone predict menstrual changes in binge eating in women with BN (Lester *et al.* 2003; Edler *et al.* 2007). Taken together, these animal and human data provide support for the modulating effect of estrogen and progesterone on food intake and body weight via the hypothalamus (Butera *et al.* 1992) and highlight their potential role in the appetite and weight disturbances in eating disorders.

Could individual differences in the activation of ovarian hormones during puberty account for the moderation of genetic effects observed in this study? Although estrogen and progesterone concentrations are heritable (Meikle *et al.* 1986; Sakai *et al.* 1991), few studies have examined associations between ovarian hormone receptor genes and eating pathology. Promising initial results have been obtained for an estrogen receptor beta gene (see Klump & Gobrogge, 2005), but replications are lacking and no studies have examined candidate genes for progesterone. Another possibility is that ovarian hormones may influence the genetic diathesis of eating pathology indirectly through their regulation of gene transcription (Ostlund *et al.* 2003) within other neuronal systems (e.g. the serotonin system) that influence food intake and/or mood (e.g. anxiety, depression; see discussion above). Serotonin is an interesting candidate in this regard, as alterations in 5-HT_{2A} receptor functioning have been observed in eating disorders (Frank *et al.* 2002; Bailer *et al.* 2004). This receptor has been shown to be more sensitive to estrogen regulation than others (Ostlund *et al.* 2003) and has been associated with AN in candidate gene studies (Klump & Gobrogge, 2005). Thus, future studies should examine the

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role of ovarian hormones in the regulation of serotonin and other neurobiological systems, as well as the direct effects of ovarian hormone receptor genes on food intake, mood, and risk for eating pathology during puberty.

Several limitations of our study should be noted. First, we were unable to investigate eating disorder diagnoses due to the low prevalence of AN and BN in our young adolescent sample (APA, 2000) and the limited power of twin moderation analyses for categorical phenotypes. Additional research is needed to determine how these findings extend to clinical eating disorders.

Secondly, our sample was too small to allow for testing multiple submodels. This may have decreased our power to detect differences between the nested models presented in Table 1. Moreover, the mean age of our twins (i.e. 14 years old) ensured that the majority of twins were in mid-to-late puberty. Decreased variability during early puberty may have limited our ability to detect genetic effects at earlier stages of development. Although *increases* in heritability were observed even at later pubertal stages, replications within larger, independent datasets are needed to confirm our observed moderation effects. As noted earlier, Rowe and co-workers (2002) did not find differences in the heritability of disordered eating across adolescence. Although methodological differences may account for discrepant results, additional research in larger twin samples with more variability in pubertal development is needed to confirm these impressions.

Finally, our data were cross-sectional, and thus we were unable to examine longitudinal associations between changes in pubertal development and increases in genetic effects. Studies that include at least annual assessments of twins throughout puberty are needed for examining these longitudinal relationships. Although MTFS data were available from baseline assessments (mean age of twins = 11 years) in addition to the follow-up data presented here (mean age = 14 years), the timing (i.e. every 3–4 years) of assessment periods made it difficult to disentangle within-subject changes in pubertal development from changes in age. This limitation was circumvented in the current study by focusing on a single assessment period where pubertal development was not associated with age ($r = 0{\cdot}01$, $p = 0{\cdot}76$; Burt *et al.* 2006). Nonetheless, our findings would be enhanced by longitudinal data collected at least annually that could examine within-subject changes in genetic effects on disordered eating across puberty. Such data would contribute to the growing knowledge of the nature of pubertal risk for eating disorders and the role of both biological and psychosocial risk factors in the development of these disorders.

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DECLARATION OF INTEREST

None.

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