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GENETIC AND ENVIRONMENTAL COMPONENTS TO SELF-INDUCED VOMITING

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Abstract

Objective—We examined the association between the genetic and environmental factors contributing to the liability to having ever engaged in self-induced vomiting (SIV initiation) and the genetic and environmental factors contributing to regular SIV behaviors (weekly or daily) for weight control.

Method—SIV was assessed in 3,942 women from monozygotic twin pairs and 2,790 women from same-sex dizygotic twin pairs, aged 20–47, from the Swedish Twin study of Adults: Genes and Environment. A causal-contingent-common pathway model assessed the extent to which genetic and environmental factors that influence initiation of SIV also influence regular SIV behaviors.

Results—In the best-fit model, genetic and individual-specific environmental factors influenced liability to SIV initiation. The genetic factors influencing regular SIV behaviors were the same as the genetic factors influencing SIV initiation. Additional individual-specific environmental factors that were unrelated to SIV initiation influenced regular SIV behaviors.

Discussion—Our findings provide evidence that the underlying liabilities for SIV initiation and regular SIV lie on the same continuum given the degree of overlap in risk between SIV initiation and regular SIV behaviors. Further, the lack of specific genetic factors and the importance of

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individual-specific environmental factors for regular SIV behaviors highlight the significance of environmental factors in the etiology of eating disorder symptomatology and the non-deterministic nature of genetic factors. Finally, our results suggest that when it comes to preventing individuals from developing regular SIV behavior, intervening at an environmental level is warranted.

Keywords

Self-induced vomiting; twin study; heritability; bulimia nervosa; purging disorder; eating disorder

Eating disorders are a serious public health concern affecting approximately 8% of women cross-nationally based on DSM-5 criteria[1] and are associated with significant psychopathology[2] and increased mortality.[3, 4] Although many individuals may experiment with disordered eating behaviors (e.g., inappropriate compensatory behaviors, binge eating), far fewer progress to engaging in these behaviors on a regular and consistent basis. It is unknown whether the same factors that influence initiation and experimentation in disordered eating behaviors also affect the regular engagement in this symptomatology. Here, we explore whether the genetic and environmental factors associated with having ever engaged in self-induced vomiting (SIV) for weight control overlap with the genetic and environmental factors associated with regular SIV behaviors.

Thirty years of twin and genetic studies have established that there is a genetic contribution to the etiology of eating disorders.[5] For example, twin studies estimate the heritability for bulimia nervosa (BN) from 28% to 83% and for anorexia nervosa (AN) from 56% to 76%.[5] The single twin study examining purging disorder (PD) also showed a significant familial component (genetic plus common environmental factors), accounting for 20% of the liability.[6]

Not only has the genetic risk for eating disorders been established via studies examining threshold or subthreshold diagnostic outcomes, dimensional or behavioral indices of the eating disorders also show a genetic component, corroborating the importance of genetic factors in their etiology.[5] One significant advantage of exploring genetic and environmental contributions to etiology at the symptom or behavioral level include the ability to explore symptoms that are transdiagnostic, such as SIV, and may be more reliably assessed than threshold diagnoses. Specifically, SIV is an eating disorder symptom that can be observed in BN, AN, and various presentations of other specified feeding and eating disorders, including PD. Moreover, SIV, as a clear behavioral marker, is the most reliably assessed behavioral feature of BN and improves the reliability of an overall BN diagnosis when assessed.[7]

Although the genetic liability to SIV has not been fully elucidated, there is evidence of a genetic component. Within the context of a BN diagnosis, SIV is the symptom most strongly influenced by genetic factors, with a heritability of 53%,[8] and the inclusion of SIV in molecular genetic linkage studies of BN enhanced the ability to detect significant genetic signals.[9] Similarly, having ever engaged in SIV, examined as a symptom independent of an eating disorder diagnosis, is 72% heritable.[10] In contrast, when the heritability of lifetime SIV was examined as a symptom independent of an eating disorder diagnosis, yet required the DSM-IV threshold of at least twice a week for three months be met, heritability was estimated at only 8%.[11] This contrast in findings may suggest that the genetic etiology of

SIV varies as a function of the presence and frequency of additional symptomatology. Despite findings suggesting that SIV is influenced, at least in part, by genetic factors, it is unknown whether the genetic (and environmental) factors that influence having ever engaged in SIV for weight and shape reasons (SIV initiation) also contribute to regularly engaging in SIV (SIV progression)—a key symptom of several threshold eating disorder diagnoses (e.g., BN, AN-binge purge type, PD).

With respect to binge eating, another key symptom of several eating disorder diagnoses, one study suggests that only 38% of the genetic and environmental factors influencing binge eating initiation are shared with a threshold diagnosis of BN and that environmental factors may be key in determining whether the initiation of binge eating progresses to a BN diagnosis.[12] Similar processes may be at play for SIV. The clarification of how genetic and environmental factors contribute to SIV initiation and SIV progression will inform our understanding of how this fundamental feature of several eating disorder diagnoses develops into a chronic behavior. Thus, the purpose of this study was to examine the extent to which the same genetic and environmental factors contribute to both the initiation of SIV, defined as having ever engaged in the behavior, and regularly engaging in SIV in females (SIV progression)—regardless of whether SIV occurs within the context of an eating disorder diagnosis.

METHOD

Participants

Women eligible for the current study were from the Swedish Twin study of Adults: Genes and Environment (STAGE) study of the Swedish Twin Registry (http://ki.se/ki/jsp/polopoly.jsp?d=9610&l=en), a large population-based sample of Swedish twins born 1959–1985.[13] Twins were between the ages of 20 and 47 years at the time of assessment. The STAGE study was approved by the Regional Ethics Committee at Karolinska Institutet and by the Biomedical Institutional Review Board at the University of North Carolina at Chapel Hill. Details of the study design are described elsewhere.[14, 15]

Zygosity—Zygosity was assigned based on responses to the following questions: (Q1) “During childhood, were you and your twin partner as like as ‘two peas in a pod’ or no more alike than siblings in general?” and (Q2) “How often did strangers have difficulty in distinguishing between you and your twin partner when you were children?” Pairs were considered monozygotic (MZ) if both members responded ‘alike as two peas in a pod’ for Q1 and ‘almost always’ or ‘often’ for Q2. If both twins responded ‘not alike’ for Q1 and ‘seldom,’ ‘almost never’, or ‘never’ for Q2, they were classified as dizygotic (DZ). All other twins were classified as ‘not determined.’ This algorithm has been validated with a panel of 47 single nucleotide polymorphisms in a random sample of 198 twin pairs. The majority of twin pairs (95%; n = 188) were correctly classified. This zygosity algorithm has also previously been validated with similar results.[14]

Measures

SIV initiation, defined as having ever engaged in SIV, and regular SIV behavior (SIV progression) were both assessed with the single question, “Have you ever made yourself vomit to control your weight or shape?.” Response options were never; once or twice; every week; and daily. Participants were scored as positive for SIV initiation if they reported having ever engaged in SIV, regardless of the frequency: participants responding once or twice, every week, or daily were all scored positive for SIV initiation. Only participants who responded never were scored as negative for SIV initiation. The responses were broken down further to delineate SIV progression. Those individuals who reported a frequency of every week or daily were scored positive for SIV progression. Participants were scored negative for SIV progression if they reported SIV frequencies of once or twice and missing if they never engaged in SIV.

Statistical Procedures

Rationale—The classic twin study assesses factors influencing liability to a latent phenotype by estimating the proportion of variance due to: (1) additive genetic effects (i.e., heritability, a^2); (2) common environmental effects (c^2); and (3) individual-specific environmental effects (e^2). The total phenotypic variance is modeled as the sum of these components ($a^2 + c^2 + e^2$). Additive genetic effects represent the cumulative impact of several genes, each resulting in a small effect, on a given trait. Common environmental effects result from etiological influences that make members of a twin pair similar regardless of zygosity (e.g., parental income). It is assumed that common environmental influences contribute equally to the resemblance of both MZ and DZ pairs. Individual-specific environmental effects are events or factors that contribute to the dissimilarity of twins within a pair. The e^2 estimate also includes measurement error. Structural equation modeling allows the determination of what proportion of phenotypic variation is attributable to genetic variation among individuals (heritability) and what proportions are due to common and individual-specific environmental factors.

Model—The causal-contingent-common (CCC) pathway model[16, 17] was used in the present study (Figure 1) and is an extension of the classic twin model described above. Previous studies have used the CCC approach to answer similar questions, such as exploring the factors that influence smoking your first cigarette versus those that contribute to becoming a regular smoker[18, 19] and those factors that contribute to binge eating versus a BN diagnosis.[12] This model is the ideal statistical model to use because it estimates of the magnitude of the association between initiation and progression, taking into account the conditional nature between SIV initiation and progression. Specifically, the model is *causal* in that it estimates a direct path from liability of SIV initiation to liability of SIV progression, which indicates the amount of covariance between initiation and progression. Since progression is dependent upon initiation (i.e., one cannot develop regular SIV behavior without ever initiating SIV), a *contingent* modeling approach is needed. The *common* pathway is that the genetic and environmental effects of initiation can influence progression only by acting through the observed phenotype of SIV initiation. The use of this method also allows for examination of the total genetic and environmental effects on SIV

initiation and progression; however, the genetic and environmental effects for SIV progression are estimated after those shared with initiation are taken into account.

The CCC model assesses the latent genetic (A_I), common (C_I), and individual-specific (E_I) environmental factors for SIV initiation; the proportion of variance in initiation accounted for by A_I, C_I, and E_I is equal to the square of the connecting paths (a_i, c_i, and e_i, respectively; Figure 1). Only participants who have indicated initiation are susceptible to progression. Thus, there are two sets of factors that influence progression: (1) those that are shared with initiation, indicated as a direct path (via a beta [b] pathway; Figure 1); and (2) genetic (A_P), common (C_P), and individual-specific (E_P) environmental factors unique to progression. If SIV initiation and progression share all factors, then b will approach unity. If SIV initiation and progression share no factors, then b will approach zero. Therefore, for SIV progression, the total proportion of variance is calculated as the amount of genetic and environmental variance explained by those influences on initiation (b^2) *plus* the proportion of variance accounted for by A_P, C_P, and E_P (which is equal to the square of the connecting path, a_p, c_p, and e_p, respectively).

Using the raw ordinal data option in Mx,[20] which allows data from twin pairs where both cotwins participated and twin pairs with missing cotwin information to be analyzed, we applied a CCC full model including estimates for three parameters for SIV initiation (a_i, c_i, and e_i), three parameters for SIV progression (a_p, c_p, and e_p), and for the path from initiation to progression (b; Figure 1). We then fitted seven nested submodels, each of which dropped a specified genetic or environmental parameter (Table 1). The best-fit model was chosen based on the difference in the minus 2 log likelihood (−2lnL) from the nested model and the full model, which, under certain regularity conditions is distributed as chi-squared, where degrees of freedom (df) are equal to the difference between the df of the nested model and the full model.[21] This likelihood ratio test statistic theory applies to the test that path b differs from zero, but not to tests of variance components, such as a^2, which cannot be negative. Thus, variance component likelihood ratio test statistics are asymptotically distributed as a 50:50 mixture of chi-squares with df=0 and df=1.[22] A nonsignificant difference suggests that there is no decrement in model fit. We also used Akaike's Information Criteria (AIC)[23] to determine the best-fit model, where the lowest AIC value indicates the optimal combination of goodness-of-fit and parsimony. If a nonsignificant difference exists between the nested model and full model, the most parsimonious model, based on AIC, is the preferred model. We report both the parameter estimates and 95% confidence intervals (CI) for the full and best-fitting models.

RESULTS

Descriptive Statistics

A total of 6,732 women responded to the question about SIV and were available for twin modeling. Our final sample included 3,942 women from MZ pairs and 2,790 women from same-sex DZ pairs. Specifically, there were 1,829 MZ and 1,289 DZ pairs with complete data and 284 MZ and 212 DZ individuals without cotwin information.

There were 487 (7.2%) women who initiated SIV (scored positive for initiation). Of these 487 women, 165 (33.9%) engaged in SIV regularly (scored positive for progression). No differences in prevalence were observed between zygosity groups [SIV initiation ($\chi^2 = 0.13$, df = 1, $p < .72$); SIV progression ($\chi^2 = 0.63$, df = 1, $p < .43$)]. There were 40 MZ and 17 DZ pairs concordant for SIV initiation. Of the 40 MZ and 17 DZ pairs concordant for SIV initiation, 8 MZ and 4 DZ pairs were concordant for SIV progression.

CCC Model

Model fit statistics for the full model and the seven nested models are presented in Table 1. Based on the χ^2 difference tests, model II (constraining $a_i = 0$, indicating that SIV initiation has no genetic contribution), could be rejected as fitting significantly worse than the full model. Of the remaining models, model VIII had the lowest AIC value, indicating that it was the best model based on a combination of goodness-of-fit and parsimony. This model estimated genetic and individual-specific environmental factors for both SIV initiation and progression, individual-specific environmental factors unique to SIV progression, and a direct path from SIV initiation to SIV progression.

Parameter estimates and 95% CI for the full and best-fitting models are presented in Table 2. Point estimates should be interpreted within the context of the CIs and number of concordant pairs. For SIV initiation, estimates from the full model were as follows: a^2 = 61% (95% CI: 29%, 70%); c^2 = 2% (95% CI: 0%, 30%); and e^2 = 37% (95% CI: 29%, 46%). The full model also suggested that a majority of the genetic and environmental factors influencing SIV initiation were shared with SIV progression as b^2 was calculated as 83% (95% CI: 1%, 99%). Specifically, all of the genetic factors influencing liability to progression were shared with SIV initiation, whereas a proportion of the variance for SIV progression was accounted for by common environmental [c^2 = 3% (95% CI: 0%, 38%)] and individual-specific environmental [e^2 = 14% (95% CI: 1%, 95%)] factors not shared with SIV initiation.

Results from the best-fitting model (model VIII) were similar. However, in the best-fit model, we were able to drop all common environmental estimates, which may suggest that individual-specific environmental factors unique to SIV progression influence whether an individual who has initiated SIV will engage in regular SIV (Table 2).

DISCUSSION

This is the first study, to our knowledge, to model the genetic and environmental associations between SIV initiation, defined as having ever engaged in SIV, and progression, defined as regularly engaging in SIV, in a population-based sample of female twins. Results indicated that genetic factors are substantial and important for SIV initiation and SIV progression. Heritability was estimated at 61% in the full model for SIV initiation and 51% for SIV progression ($a_i^2 \times b^2$; 61% × 0.83). These estimates are consistent with previous studies suggesting substantial genetic influence to SIV and that SIV is the most heritable BN symptom.[8,10] However, this estimate is higher than the familial nature (additive genetic plus common environmental factors) previously estimated for PD (20%).[6] This difference in estimates may be due to the fact the previous report combined several compensatory

behaviors (e.g., SIV, laxative use) as purging methods and we examined the engagement in SIV as an independent behavior, not within the context of a threshold eating disorder diagnosis—which requires additional criteria (e.g., body dissatisfaction).

Approximately one-third of the individuals in our sample who initiated SIV also regularly engaged in SIV. Our findings provide evidence that the underlying liabilities for SIV initiation and progression lie on the same continuum. Intriguingly, no new genetic factors emerged that contribute to SIV progression—100% of the genetic factors influencing liability to SIV progression were shared with SIV initiation. In contrast, a small proportion of liability to SIV progression was attributed to environmental factors that were unique to SIV progression and not shared with initiation. It seems that while additive genetic factors influence the propensity to initiate SIV as a method of controlling weight and shape, environmental factors (versus genetic factors) are important in determining whether, after initiation, this behavior becomes a regular occurrence. Further, given that we were able to drop the common environmental estimates in the best-fit model, this may suggest that individual-specific environmental factors are more important in moving from SIV initiation to regular behavior. This is in line with a previous CCC model investigation of binge eating and BN, which also suggested that individual-specific environmental factors are important in the progression to BN once binge eating is initiated.[12]

Indeed, genetic factors are important in the etiology of SIV for weight control purposes; however, environmental factors, which themselves may be genetically mediated, have also been implicated. For example, sociocultural pressure for thinness can promote internalization of a thin ideal in genetically vulnerable individuals,[24] which, in turn, can prompt body dissatisfaction and efforts to control weight and shape.[25] In other words, genetic vulnerability to thin ideal internalization might set the stage for a chain reaction increasing the risk for SIV initiation and progression; however, once a person initiates SIV, environmental factors, such as this sociocultural pressure for thinness, influence the transition to regular behavior. Moreover, these environmental factors may also interact with the genetic propensity to engage in extreme weight control behaviors such as SIV. For example, thinness expectancies (e.g., over-valuation of the role that thinness plays in success or quality of life) predict both SIV and binge eating longitudinally.[26] Peer groups are also proximal environmental influences that might interact with genetic liability to increase vulnerability to SIV such that members of female friendship groups share similar levels of weight concern, dieting, binge eating, and SIV.[27, 28] Although gene by environment interactions cannot be teased apart in the CCC model, unmeasured gene by individual-specific environment interactions are subsumed within individual-specific environmental variance.[29] Thus, a portion of the individual-specific environmental effects unique to SIV progression may include gene by individual-specific environment interactions.

Finally, our observed pattern of results differs from those observed in CCC models of substance use, in which new genetic factors (i.e., genetic factors independent of those that contributed to initiation) play a more prominent role in whether initiation progresses to regular use.[18, 30, 31] Although several twin studies indicate a shared genetic component between eating and substance use disorders and their symptomatology, these factors are not entirely shared.[3234] Thus, some of these non-overlapping genetic factors may be related to

biological or genetic vulnerability differences specifically in the path from initiation to progression. An individual's physiological response to prolonged use of a specific substance and thus propensity to become physiologically addicted could presumably enact differential biological or genetic responses in the brain, for example,[35] than SIV enacts. This may be evidenced by the physical symptoms of withdrawal and tolerance observed with physiological substance dependence that does not necessarily occur with abstinence from SIV.

This study should be considered within the context of its limitations. SIV is a low base rate behavior, which occurred in only 7.2% of our sample, thus limiting power to detect effects. Only a relatively small number of twins reported engaging regularly in SIV, resulting in wide confidence intervals for parameter estimates. Because of the lack of power, we might not have been able to detect significant genetic factors for SIV progression. At best, we can say that at least some (perhaps all) of the genetic factors contributing to SIV initiation also contribute to SIV progression. In addition, low power limits our ability to detect significant common environmental effects. Further, we defined SIV initiation and progression from the same item, assessed at a single time point, so we were unable to capture initiation (the first time a behavior occurred) and progression (the point in time when the behavior transitions from initiation to regular behavior) time points. However, because the model is a contingent approach where progression is dependent upon initiation, we are still able to differentiate the genetic and environmental effects for having ever engaged in SIV versus regular SIV behavior.

This sample is also comprised solely of Caucasian female twins, which may limit generalizability of our findings to diverse racial groups, men, or non-twins. However, initial reports suggest no differences in genetic risk for bulimic behaviors between African Americans and European Americans[34] or mean differences between twins and singletons for disordered eating behavior.[36] Notwithstanding these limitations, this study has three important strengths including the use of a large, population-based sample and use of the CCC model. The CCC model is an improvement on previous examinations of the heritability of SIV because it takes into account the contingent nature between having ever engaged in the behavior and regularly engaging in the behavior. Finally, this is one of the first studies to examine the extent to which the same or different genetic and environmental factors contribute to the initiation and progression of SIV as an isolated symptom, not requiring a threshold eating disorder diagnosis or frequency criterion to be met.

The propensity to ever engage in SIV for weight control purposes and to regularly engage in SIV are driven substantially by genetic factors and the genetic factors influencing SIV progression may be entirely shared with SIV initiation. Although a majority of the factors influencing SIV progression are shared with initiation, individual-specific environmental factors unique to SIV progression appear important in determining whether an individual regularly engages in SIV. Our findings lend additional support to the conceptualization of eating disorders as dimensional versus categorical given the degree of overlap in risk factors between having ever tried this behavior and the development of regular symptoms. Given the challenges that can come with diagnostic classification (e.g., changing diagnostic definitions over time), examination of the genetic and environmental contributions to specific eating

disorder symptoms (e.g., SIV, binge eating) is indicated.[37] Further, this approach will aide in the development of novel prevention and clinical interventions. The lack of new genetic factors and importance of individual-specific environmental factors on SIV progression highlights the importance of environmental factors in the etiology of eating disorder symptomatology and the non-deterministic nature of genetic factors; thus, intervening at the environmental-level when it comes to breaking the chain of SIV initiation becoming a regular behavior is critical. Only through the continued investigation of transdiagnostic eating disorder symptoms will we be able to deconstruct eating disorder diagnoses into their component symptoms and provide targeted prevention and intervention programs designed to address the specific risk factors involved in initiation versus maintenance.

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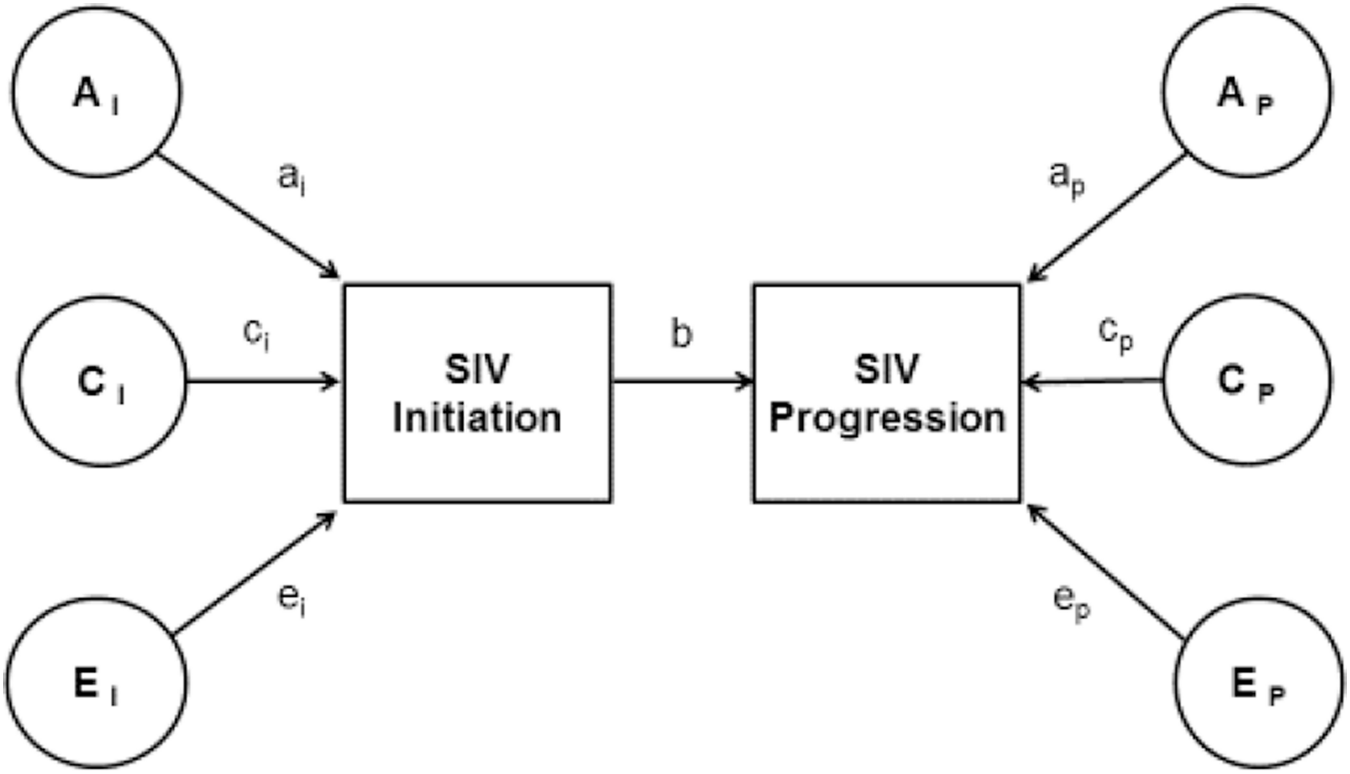

Figure 1. Causal-contingent-common pathway model

Note. SIV = self-induced vomiting. Genetic (A or a), shared environmental (C or c), and individual-specific environmental (E or e) factors are presented for the two stages of SIV. The subscript “I” (or “I”) refers to initiation of (SIV), whereas the subscript “P” (or “p”) refers to progression of SIV. The path coefficient “b” represents the pathway from initiation to progression of SIV.

Table 1

Model description and fit statistics for the full (model I) causal-contingent-common pathway model and nested (models II – VII) for self-induced vomiting behavior.

Model No.	Model Description	Model	−2lnL	df	χ^2 diff (df)	AIC
I	Full model	$a_i c_i e_i - a_p c_p e_p$, b	4550.59	7366	---	−10181.41
II	Genetic factors for progression set to 0	$a_i c_i e_i - c_p e_p$, b	4550.59	7367	0.00 (1)	−10183.41
III	Genetic factors for initiation set to 0	$c_i e_i - a_p c_p e_p$, b	4565.40	7367	14.81 (1)*	−10168.60
IV	Common environmental factors for progression set to 0	$a_i c_i e_i - a_p e_p$, b	4550.67	7367	0.08 (1)	−10183.33
V	Common environmental factors for initiation set to 0	$a_i e_i - a_p c_p e_p$, b	4550.60	7367	0.01 (1)	−10183.40
VI	Common environmental factors for initiation set to 0 Common environmental factors for progression set to 0	$a_i e_i - a_p e_p$, b	4550.68	7368	0.09 (2)	−10185.32
VII	Genetic factors for progression set to 0 Common environmental factors for progression set to 0	$a_i c_i e_i - e_p$, b	4550.67	7368	0.09 (2)	−10185.33
VIII	**Common environmental factors for initiation set to 0 Genetic factors for progression set to 0 Common environmental factors for progression set to 0**	**$a_i e_i - e_p$, b**	**4550.68**	**7369**	**0.09 (3)**	**−10187.32**

Note. AIC = Akaike's Information Criterion (Akaike, 1987); −2lnL = −2 log likelihood; df = degrees of freedom;

*= p < .01. ace = additive genetic, shared (or common) environment, and individual-specific environmental effects model; ae = additive genetic and individual-specific environmental effects model; e = individual-specific environmental effects model; b = pathway from initiation to progression. The best-fitting model is indicated in bold-type.

Table 2

Causal-contingent-common pathway model parameter estimates (95% confidence interval) for full and best fit models for self-induced vomiting.

		Initiation			Progression			
Model No.	**Model**	**a^2**	**c^2**	**e^2**	**b^2**	**a^2**	**c^2**	**e^2**
I	$a_ic_ie_i - a_pc_pe_p$, b	61% (29%, 70%)	2% (0%, 30%)	37% (29%, 46%)	83% (1%, 99%)	0% (0%, 0%)	3% (0%, 38%)	14% (0%, 95%)
VIII	**$a_ie_i - e_p$, b**	**63% (54%, 70%)**	**---**	**37% (30%, 47%)**	**85% (4%, 99%)**	**---**	**---**	**15% (1%, 96%)**

Note. For each model, the first set of parameters (ACE) refers to initiation and the second set to progression. For progression, estimates are residual values, unique to progression after the genetic and environmental influences of initiation are accounted for. Values represent standardized parameters estimates with 95% confidence intervals in parentheses. ace = additive genetic, shared (or common) environment, and individual-specific environmental effects model; ae = additive genetic and individual-specific environmental effects model; e = individual-specific environmental effects model; b = pathway from initiation to progression. The best-fitting model is indicated in bold-type.