The Relationship Between the Genetic and Environmental Influences on Common Externalizing Psychopathology and Mental Wellbeing

Kenneth S. Kendler[1,2,3], **John M. Myers**[1,2], and **Corey L. M. Keyes**[4]

[1]Virginia Institute of Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, United States of America

[2]Department of Psychiatry, Virginia Commonwealth University School of Medicine, United States of America

[3]Department of Human and Molecular Genetics, Virginia Commonwealth University School of Medicine, United States of America

[4]Department of Sociology, Emory University, United States of America

Abstract

To determine the relationship between the genetic and environmental risk factors for externalizing psychopathology and mental wellbeing, we examined detailed measures of emotional, social and psychological wellbeing, and a history of alcohol-related problems and smoking behavior in the last year in 1,386 individual twins from same-sex pairs from the MIDUS national US sample assessed in 1995. Cholesky decomposition analyses were performed with the Mx program. The best fit model contained one highly heritable common externalizing psychopathology factor for both substance use/abuse measures, and one strongly heritable common factor for the three wellbeing measures. Genetic and environmental risk factors for externalizing psychopathology were both negatively associated with levels of mental wellbeing and accounted for, respectively, 7% and 21% of its genetic and environmental influences. Adding internalizing psychopathology assessed in the last year to the model, genetic risk factors unique for externalizing psychopathology were now *positively* related to levels of mental wellbeing, although accounting for only 5% of the genetic variance. Environmental risk factors unique to externalizing psychopathology continued to be negatively associated with mental wellbeing, accounting for 26% of the environmental variance. When both internalizing psychopathology and externalizing psychopathology are associated with mental wellbeing, the strongest risk factors for low mental wellbeing are genetic factors that impact on both internalizing psychopathology and externalizing psychopathology, and environmental factors unique to externalizing psychopathology. In this model, genetic risk factors for externalizing psychopathology predict, albeit weakly, higher levels of mental wellbeing.

Keywords

wellbeing; substance abuse; externalizing disorders; twin studies

A wide range of family, twin and adoption studies support an important role for genetic factors in the etiology of common externalizing psychopathology typically characterized by psychoactive substance use and misuse, and conduct and antisocial behaviors (Eissenberg & Balster, 2000; Mayfield et al., 2008; Tuvblad et al., 2005). Furthermore, these disorders typically cluster together in general population samples (Krueger et al., 2005; Krueger et al., 2001) and several large-scale twin studies have shown that their genetic risk factors are closely interrelated (Kendler et al., 2003; Kendler et al., 2011a; Hicks et al., 2004; Hicks et al., 2011). For convenience, we will here consider these disorders as manifestations of 'externalizing psychopathology'.

This inter-related group of disorders can be usefully contrasted with what has been termed 'internalizing psychopathology' which consists most typically of common mood and anxiety disorders. Like externalizing psychopathology, internalizing psychopathology appears to be substantially influenced by genetic factors (Sullivan et al., 2000; Kendler et al., 2006; Hettema et al., 2001) that appear to be closely inter-related (Kendler et al., 2003; Kendler et al., 2011a). In population samples, externalizing psychopathology and internalizing psychopathology are modestly to moderately positively inter-correlated (Krueger, 1999), and part of this correlation is a result of shared genetic risk factors (Kendler et al., 2003; Kendler et al., 2011a).

Many studies have examined the role of genetic influences on various measures of wellbeing (e.g., happiness, life satisfaction or subjective wellbeing; Lykken & Tellegen, 1996; Stubbe et al., 2005; Roysamb et al., 2003; Nes et al., 2006), and have consistently found modest to moderate levels of heritability. These findings lead to an obvious question: What is the relationship between the genetic influences on mental wellbeing and psychopathology? This question is of interest because it sheds light on the degree to which, from a genetic perspective, mental health reflects something positive in its own right versus simply the absence of high risk for mental illness, or what Keyes refers to as the two (or dual) continua model of mental health and illness (Keyes, 2002; Keyes, 2005).

Previously, we examined the relationship between last year internalizing psychopathology and mental wellbeing in the MIDUS Twin Registry — a US national probability sample (Kendler et al., 2011b). We showed that no more than half of the genetic liability underlying a latent variable measure of mental wellbeing (indexed by specific measures of social, psychological and emotional wellbeing) was shared with a latent variable measure of internalizing psychopathology indexed by last year history of major depression, generalized anxiety disorder and panic attacks. In short, the absence of genetic risk for internalizing psychopathology does not mean the presence of a strong genetic liability for mental wellbeing, which supports Keyes' two continua model.

In this report, we follow up on this earlier effort and look first at the association of the genetic and environmental risk factors for externalizing psychopathology in the MIDUS registry — indexed by last year alcohol problems and smoking frequency. Our prediction was that high levels of externalizing psychopathology would be associated with lower levels of mental wellbeing and that probably this would be mediated through both genetic and environmental paths. Second, we performed a joint twin analysis of internalizing psychopathology, externalizing psychopathology and mental well-being designed to determine, controlling for levels of internalizing psychopathology, the unique association between externalizing psychopathology and mental well-being, and the degree to which that was mediated through genetic or environmental paths. Again, our prediction was that externalizing psychopathology would continue to have a negative association with mental wellbeing; however, the expected magnitude of that unique association was less clear to us.

Methods

Sample

About 50,000 households that were representative of the US population were screened by telephone to determine if they knew of immediate relatives who were members of twin pairs. Inclusion criteria included being first-degree relatives of the original contact or the contact's partner, being between 25 and 74 years old at the time of recruitment, living in the continental United States, being reachable by telephone, and being fluent in English. 14.8% of screened households had twin pairs, of which 60% gave permission for the twins to be contacted. Zygosity was determined using self-report questions shown to predict zygosity with greater than 90% accuracy (Lykken et al., 1990). The ethnic composition of the same-sex twin sample was 84.7% White (non-Hispanic), 4.4% Black, and 1.8% 'other' minority (the remaining percent are refusals to answer).

The MIDUS survey complied with Institutional Review Board standards of the University of Wisconsin and of the Harvard Medical School, and interviewers read to the interviewees a standard informed consent protocol at the beginning of the telephone interview.

The twin sample examined in this report included a total of 1,386 twins from same-sex twin pairs. Given the low power to detect qualitative sex effects (Prescott & Gottesman, 1993), we excluded opposite-sex dizygotic twins from this analysis. The resulting sample contained 670 complete pairs (46 individual twins without their co-twin). The 49 same-sex twin pairs (or 98 individual twins from a same-sex pair) that are missing from the present analyses come from 23 twin pairs (or 46 individual twins) without their co-twin and 26 twin pairs (or 52 individual twins) with missing data on one of the measures of mental illness or mental well-being.

The complete same-sex twin pairs were divided into the following groups: 186 female monozygotic (MZ), 198 female dizygotic (DZ), 163 male MZ, and 123 male DZ, and had a mean age of 44.6 (SD = 12.2).

Measures

We utilized three measures of mental wellbeing, employing the terminology developed by Keyes (Keyes, 1998; Keyes, 2002; Keyes, 2005; Robitschek & Keyes, 2009) based on his and others' (Gallagher et al., 2009) studies of the structure of wellbeing: emotional, psychological and social wellbeing. Emotional wellbeing was assessed by a six-item scale of positive affect and an item measuring overall life satisfaction (Bradburn, 1969; Gurin et al., 1960; Mroczek & Kolarz, 1998; Cantril, 1965; Andrews & Withey, 1976). The Cronbach alpha reliability of this 7-item emotional wellbeing scale was +0.88. Psychological wellbeing was assessed by six scales of 3 items each (Table 1) (Ryff & Keyes, 1995). The Cronbach alpha reliability of the psychological well-being scale was +0.76. Social well-being was assessed with 5 scales of 3 items each (Table 1). The Cronbach alpha reliability of the social wellbeing scale was +0.72 (Keyes, 1998).

In the 1995 MIDUS survey, alcohol problems were assessed by the 5-item version of the Michigan Alcohol Screening Test (Selzer, 1971). Tobacco consumption in the last year was assessed by three questions, the results of which were collapsed into one 3-item variable: non-smoker, smoking < 20 cigarettes per day, and smoking > 20 cigarettes per day.

This same assessment also included a past year history of major depression (MD), generalized anxiety disorder (GAD), and panic attacks (PA), which was assessed by phone interview using the highly structured Composite International Diagnostic Interview Short Form (CIDI-SF; Kessler et al., 1998). Studies have shown that this instrument has excellent

diagnostic sensitivity and diagnostic specificity as compared with the DSM-IV diagnoses based on the full CIDI in the National Comorbidity Study (Kessler et al., 1999).

Statistical Methods

Last year MD, GAD and PA were treated as dichotomous threshold traits. Alcohol abuse and the three dimensions of mental wellbeing were treated as 5-category poly-chotomies, and cigarette use was treated as a 3-category polychotomy. We examined the relationship between the genetic and environmental influences on externalizing psychopathology and mental wellbeing in two ways. First, we fitted a bivariate Cholesky model with externalizing psychopathology as the upstream (or independent) variable, and mental wellbeing as the downstream (or dependent) variable. Second, we added internalizing psychopathology as the most upstream variable so that, in this model, the cross-genetic and environmental pathways from externalizing psychopathology to mental wellbeing represented the impact of risk factors unique to externalizing psychopathology (i.e., not shared with internalizing psychopathology). Per results in our prior study (Kendler et al., 2011b), externalizing psychopathology, internalizing psychopathology and mental wellbeing are treated in our analyses as latent variables in a common factor model.

In studying both same-sex male and female twins, we can test for quantitative sex effects, allowing us to determine if the magnitude of the genetic and environmental parameters in our structural model differ between sexes. Twin model fitting of the raw data was performed using the Mx software package (Neale et al., 2003). The goal of model fitting is to achieve a balance between explanatory power and simplicity. This goal is operationalized by the use of Bayesian information criterion (BIC) that has been shown to perform particularly well with complex models, as we have used here (Markon & Krueger, 2004). We seek to *minimize* the BIC value.

Results

Externalizing Psychopathology and Mental Well-being

Our first set of twin models examined the inter-relationship between our three measures of mental wellbeing and our two measures of externalizing psychopathology in the 1995 MIDUS survey data. Our baseline model I was a saturated ACE Cholesky decomposition, which included separate parameter estimates for males and females (Table 2). Model II dropped all shared environmental pathways and resulted in a large improvement in the BIC (−48.5). Model III dropped all genetic pathways and also resulted in an improvement in fit over model I, but was inferior to the fit provided by model II. In model IV, we then constrained all the parameters in model II to equality across the sexes, producing a further substantial improvement in fit (BIC = −87.9). Model IV was our best fit model and the parameter estimates are given in Figure 1.

Cigarette usage and alcohol problems both loaded relatively strongly on the externalizing psychopathology factor (with loadings of +0.61 and +0.40, respectively). However, both measures also had substantial genetic specific effects. The latent externalizing psychopathology factor was highly heritable with an estimated a^2 of 0.96. (While unexpectedly high, the 95% CIs of this estimate were broad [0.14–1.00] and consistent with prior estimates of the heritability of a latent externalizing factors — for example, ~ 0.75 in Hicks et al. [2011].) The loadings on the latent mental wellbeing factor were similar to those reported previously (Kendler et al., 2011b), with the strongest loading for psychological wellbeing, followed by social and emotional wellbeing.

Of greatest interest to us, the cross paths from both the genetic and environmental risk factors for externalizing psychopathology to mental wellbeing were both modest and

negative (−0.23 and −0.24, respectively). This model estimated the total heritability of our latent mental wellbeing variable to equal 73%, of which only 7% arises from genetic risk factors shared with externalizing psychopathology. Of the 27% of variance in liability to mental wellbeing that was environmental, 21% arose from environmental risk factors for externalizing psychopathology.

Using the best-fit model to decompose the association between the two latent externalizing psychopathology and mental wellbeing factors resulted in an estimated correlation of −0.28, of which 82% was a result of genetic, and 18% of environmental, factors.

Externalizing and Internalizing Psychopathology and Mental Wellbeing

In our second set of analyses, we explored how the inclusion of measures of internalizing psychopathology impact on the association between externalizing psychopathology and mental wellbeing. We again used a Cholesky decomposition ordering the variables as follows: internalizing psychopathology, externalizing psychopathology and mental wellbeing. In this way, the genetic and environmental cross paths from externalizing psychopathology to mental wellbeing represent the unique association between the two variables controlling for the impact of genetic or environmental factors shared in common between internalizing psychopathology and externalizing psychopathology.

Our baseline model I was a saturated ACE Cholesky decomposition that included separate parameter estimates for males and females (Table 3). Model II dropped all shared environmental pathways and resulted in a large improvement in the BIC (−85.3). Model III dropped all genetic pathways and also resulted in an improvement in fit over model I, but was inferior to the fit provided by model II. In model IV, we constrained all the parameters in model II to equality across the sexes, producing a large improvement in fit (BIC = −156.3). Model IV was our best-fit model and the parameter estimates are given in Figure 2.

The genetic factors that are shared between internalizing psychopathology and externalizing psychopathology (factor A1) are substantially and inversely correlated with levels of mental wellbeing (i.e., a cross path of −0.57). Surprisingly, the A2 factor, which indexes genetic effects unique to externalizing psychopathology, loads modestly but *positively* on mental wellbeing (i.e., a cross path of +0.18). Environmental factors that impact on both internalizing psychopathology and externalizing psychopathology (E1) are modestly and inversely associated with level of mental wellbeing (i.e., a cross path of −0.11). Similarly, the E2 factor, which indexes environmental effects unique to externalizing psychopathology, loads moderately and negatively on mental wellbeing (i.e., a cross path of −0.27). Thus, controlling for the risk factors shared with internalizing psychopathology and externalizing psychopathology, genetic factors unique to externalizing psychopathology tend to predispose individuals to higher mental wellbeing at the same time the environmental risk factors unique to externalizing psychopathology tend to predispose individuals to lower mental well-being.

The best-fit model depicted in Figure 2 estimates a total heritability of mental wellbeing of 72%, of which approximately 50% is unique to mental wellbeing, 5% shared only with externalizing psychopathology, and 45% shared with both internalizing psychopathology and externalizing psychopathology. Of the environmental causes that contribute to mental wellbeing (total of 28% of variance in liability), 26% was unique to externalizing psychopathology and only 4% share both with internalizing psychopathology and externalizing psychopathology.

Discussion

The goal of this article was to determine the association between genetic and environmental risk factors for externalizing psychopathology and mental wellbeing in a population-based twin sample that is broadly representative of the US population. Results of our first bivariate analysis of externalizing psychopathology and mental wellbeing were relatively straightforward. The externalizing psychopathology common factor was modestly and negatively related to mental wellbeing, and this association was largely mediated via genetic factors. These results can be usefully compared with those we found previously in the same sample with internalizing psychopathology (Kendler et al., 2011b). Most notably, the magnitude of the association with mental wellbeing was much stronger for internalizing psychopathology (−0.54) than we found for externalizing psychopathology (−0.28). Moreover, the magnitude of the genetic cross-path of mental wellbeing with internalizing psychopathology was much stronger (−0.60) than the cross path of MWP and externalizing psychopathology (−0.23). When examined individually, the genetic association between externalizing psychopathology and mental wellbeing is much weaker than that observed between internalizing psychopathology and mental wellbeing.

Our second set of analyses, which examined the association between externalizing psychopathology and mental wellbeing controlling for the effects of internalizing psychopathology, produced more surprising results. Genetic risk factors shared between internalizing psychopathology and externalizing psychopathology predicted lower levels of mental wellbeing, with a robust cross-path of −0.57. The next strongest predictor was environmental risk factors unique to externalizing psychopathology, with a cross path of −0.27 with mental wellbeing. Environmental risk factors shared between internalizing psychopathology and externalizing psychopathology had a weak impact on mental wellbeing (−0.11). Most surprising was that controlling for internalizing psychopathology, genetic risk factors for externalizing psychopathology predicted *higher* levels of mental wellbeing, with a cross path of +0.18, albeit only explaining 5% of the genetic variance for mental wellbeing.

While the positive association between the unique genetic risk for externalizing psychopathology and mental wellbeing might at first appear surprising, prior studies do document an association between both tobacco and/or alcohol consumption and wellbeing directly (Lang et al., 2007), or with several traits which are themselves correlated with mental wellbeing — particularly extraversion (Kendler et al., 1999), social support (Newcomb & Bentler, 1988) and popularity (Diego et al., 2003; Valente et al., 2005; Dubow et al., 2008). Furthermore, it is at least plausible that mental wellbeing and psychoactive drug use might both be positively related to variation in those brain processes that instantiate feelings of pleasure and happiness (Kringelbach & Berridge, 2009).

While further research will be needed to clarify the underlying processes, we speculate that the negative associations between drug use and misuse, and mental wellbeing are being captured by two other parts of the model. First, the genetic risk factors for externalizing psychopathology that are shared with internalizing psychopathology may reflect that part of the genetic vulnerability to externalizing psychopathology that predisposes to the negative sequelae of substance use (e.g., increased risk for depression and anxiety) that decrease mental wellbeing. Second, the environmental predictors of externalizing psychopathology may index the range of psychosocial adversities that predispose to drug use and misuse, and in turn decrease mental wellbeing. If correct, these two processes would 'capture' the negative associations between externalizing psychopathology and mental wellbeing, leaving the more positive elements (e.g., predisposition to extraversion, social support and

popularity) as specific genetic risks for externalizing psychopathology that are predictive of higher levels of mental wellbeing.

Limitations

First, the sample size of twins is modest, so we have limited power to detect subtle effects and our parameter estimates have wide confidence intervals (Neale et al., 1994). Second, the twins were ascertained indirectly via relatives, so we cannot be certain that biases did not creep into this process. Third, our measure of externalizing psychopathology was limited to alcohol-related problems and smoking. Measures were available in MIDUS for illicit drug use, but efforts to include this variable in our externalizing psychopathology construct were unsuccessful because of its rarity. No measures for last year antisocial behavior were collected. The lower phenotypic and genetic correlation observed between externalizing psychopathology and mental wellbeing compared to that found for internalizing psychopathology and mental wellbeing could be due to some degree to the paucity of measures in MIDUS for externalizing psychopathology compared to internalizing psychopathology. However, our externalizing psychopathology common factor was coherent and highly heritable and in a range of other samples, genetic risk for substance use and misuse was strongly correlated with genetic risk for conduct and antisocial disorders (Kendler et al., 2003; Kendler et al., 2011a).

Acknowledgments

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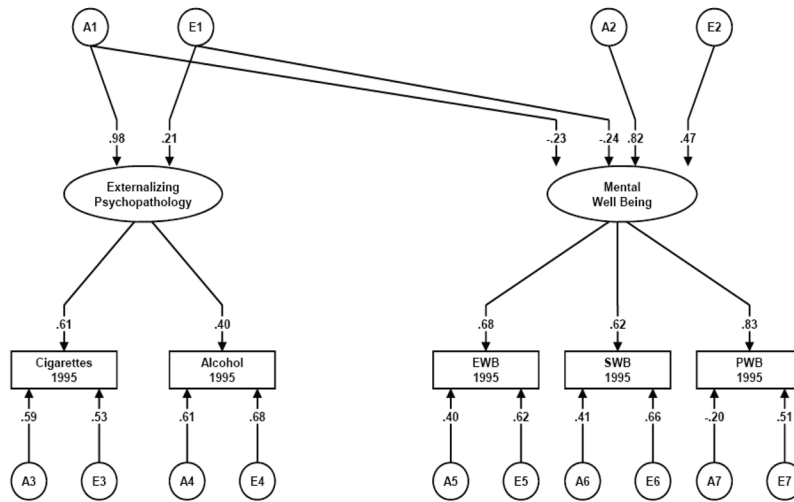
FIGURE 1.
Parameter estimates and 95% confidence intervals for the best fitting model for
Externalizing Psychopathology and Mental Well-Being in the 1995 MIDUS survey (Model
IV in table 2).
Note: A refers to additive genetic effects and E to individual specific environmental effects.
Other abbreviations are: EWB — emotional wellbeing, SWB — social wellbeing, and PWB
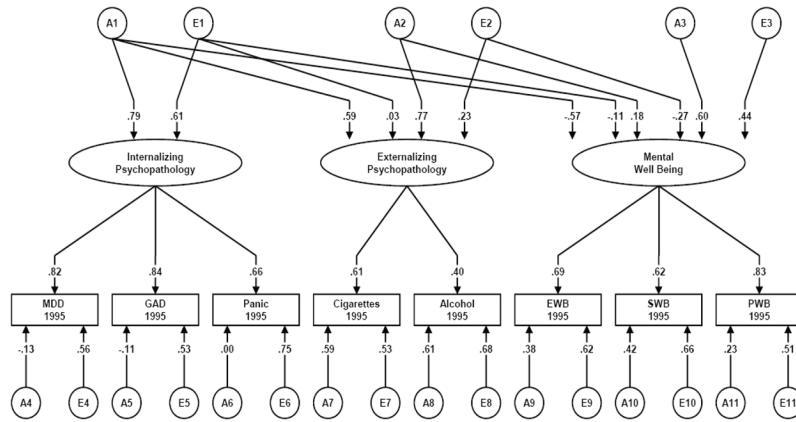— psychological wellbeing.

FIGURE 2.
Parameter estimates and 95% confidence intervals the best fitting model for Internalizing Psychopathology, Externalizing Psychopathology and Mental Well-Being in the 1995 MIDUS survey (Model IV in Table 3).
Note: A refers to additive genetic effects and E to individual specific environmental effects. Other abbreviations are: MD — major depression disorder, GAD —generalized anxiety disorder, Panic — panic attacks, EWB — emotional wellbeing, SWB — social wellbeing, and PWB — psychological wellbeing.

TABLE 1

Measures of Components of the Three Dimensions of Mental Wellbeing

Emotional Wellbeing	Psychological Wellbeing	Social Wellbeing
Positive Affect: During the last 30 days, how much of the time — *All*, *Most*, *Some*, *A little*, or *None of the time* — did you feel … (1) Cheerful, (2) In good spirits, (3) Extremely happy, (4) Calm and peaceful, (5) Satisfied, and (6) Full of life	Self-Acceptance: 1 I like most parts of my personality. 2 When I look at the story of my life, I am pleased with how things have turned out so far. 3 In many ways, I feel disappointed about my achievements in life. (−)	Social Acceptance: 1 People who do a favor expect nothing in return. 2 People do not care about other people's problems. (−) 3 I believe that people are basically kind.
Life Satisfaction: 1 Rate your life overall these days on a scale from 0 to 10, where 0 = *Worst possible life overall* and 10 = *The best possible life overall.*	Personal Growth: 1 For me, life has been a continuous process of learning, changing, and growth. 2 I think it is important to have new experiences that challenge how I think about myself and the world. 3 I gave up trying to make big improvements changes in my life a long time ago. (−)	Social Growth: 1 The world is becoming a better place for everyone. 2 Society has stopped making progress. (−) 3 Society isn't improving for people like me. (−)
	Purpose in Life: 1 Some people wander aimlessly through life, but I am not one of them. 2 I live life one data at a time and don't really think about the future. (−) 3 I sometimes feel as if I've done all there is to do in life. (−)	Social Contribution: 1 I have something valuable to give to the world. 2 My daily activities do not create anything worth- while for my community. 3 I have nothing important to contribute to society. (−)
	Environmental Mastery: 1 The demands of everyday life often get me down. (−) 2 In general, I feel I am in charge of the situation in which I live. 3 I am good at managing the responsibilities of daily life.	Social Coherence: 1 The world is too complex for me. (−) 2 I cannot make sense of what's going on in the world. (−) 3 I find it easy to predict what will happen next in society.
	Autonomy: 1 I tend to be influenced by people with strong opinions. (−) 2 I have confidence in my own opinions, even if they are different from the way most other people think. 3 I judge myself by what I think is important, not by the values of what others think is important	Social Integration: 1 I don't feel I belong to anything I'd call a community. (−) 2 I feel close to other people in my community. 3 My community is a source of comfort.
	Positive Relations with Others: 1 Maintaining close relationships has been difficult and frustrating for me.(−) 2 People would describe me as a giving person, willing to share my time with others. 3 I have not experienced many warm and trusting relationships with others. (−)	

Note: A negative sign in parenthesis indicates this item is reverse coded before summed together with the remaining items. Response options for the Psychological and Social Well-Being scales ranged from *Strongly disagree* (1), *Moderately disagree* (2), or *Slightly disagree* (3) to *Neither agree nor disagree* (4), *Slightly agree* (5), *Moderately agree* (6), to *Strongly agree* (7).

TABLE 2

Model Fitting Results for Externalizing Psychopathology and Mental Well-Being

Model	Description	$\Delta\chi^2$	Δ^{df}	Δ^{BIC}
I	Fully Saturated Cholesky Decomposition — ACE[#]	—	—	—
II	Fully Saturated Cholesky Decomposition — AE	8.1	16	−48.5
III	Fully Saturated Cholesky Decomposition — CE	29.1	16	−38.0
IV [*]	Model II + all parameters equal in males and females	21.2	30	−87.9

Note:

[#] −2loglikelihood = 13,920.1; df = 6,076; BIC = −12,998.0;

[*] best fit model.

TABLE 3

Model Fitting Results for Association between Externalizing Psychopathology and Well-Being Controlling for the Impact of Internalizing Psychopathology

Model	Description	$\Delta\chi^2$	Δ^{df}	Δ^{BIC}
I	Full Model — ACE[#]	—	—	—
II	Full Model — AE	13.5	28	−85.3
III	Full Model — CE	29.2	28	−77.5
IV[*]	Model II + all parameters equal in males and females	35.8	53	−156.3

Note:

[#] −2loglikelihood=15,672.9; df=10194; BIC= −25,669.6;

[*] best fit model.