Original Investigation

The Phenotypic and Genetic Structure of Depression and Anxiety Disorder Symptoms in Childhood, Adolescence, and Young Adulthood

Monika A. Waszczuk, MSc; Helena M. S. Zavos, PhD; Alice M. Gregory, PhD; Thalia C. Eley, PhD

IMPORTANCE The *DSM-5* classifies mood and anxiety disorders as separate conditions. However, some studies in adults find a unidimensional internalizing factor that underpins anxiety and depression, while others support a bidimensional model where symptoms segregate into distress (depression and generalized anxiety) and fear factors (phobia subscales). However, little is known about the phenotypic and genetic structure of internalizing psychopathology in children and adolescents.

OBJECTIVE To investigate the phenotypic associations between depression and anxiety disorder symptom subscales and to test the genetic structures underlying these symptoms (*DSM-5*–related, unidimensional and bidimensional) across 3 developmental stages: childhood, adolescence, and early adulthood.

DESIGN, SETTING, AND PARTICIPANTS Two population-based prospective longitudinal twin/sibling studies conducted in the United Kingdom. The child sample included 578 twins (mean age, approximately 8 and 10 years at waves 1 and 2, respectively). The adolescent and early adulthood sample included 2619 twins/siblings at 3 waves (mean age, 15, 17, and 20 years at each wave).

MAIN OUTCOMES AND MEASURES Self-report symptoms of depression and anxiety disorders.

RESULTS Phenotypically, when controlling for other anxiety subscales, depression symptoms were only associated with generalized anxiety disorder symptoms in childhood (r = 0.20-0.21); this association broadened to panic and social phobia symptoms in adolescence (r = 0.17-0.24 and r = 0.14-0.16, respectively) and all anxiety subscales in young adulthood (r = 0.06-0.19). The genetic associations were in line with phenotypic results. In childhood, anxiety subscales were influenced by a single genetic factor that did not contribute to genetic variance in depression symptoms, suggesting largely independent genetic influences on anxiety and depression. In adolescence, genetic influences were significantly shared between depression and all anxiety subscales in agreement with *DSM-5* conceptualization. In young adulthood, a genetic internalizing factor influencing depression and all anxiety subscales emerged, alongside a small significant genetic fear factor.

CONCLUSIONS AND RELEVANCE These results provide preliminary evidence for different phenotypic and genetic structures of internalizing disorder symptoms in childhood, adolescence, and young adulthood, with depression and anxiety becoming more associated from adolescence. The results inform molecular genetics research and transdiagnostic treatment approaches. The findings affirm the need to continue examining the classification of mood and anxiety disorders in diagnostic systems.

JAMA Psychiatry. 2014;71(8):905-916. doi:10.1001/jamapsychiatry.2014.655
Published online June 11, 2014.

Supplemental content at jamapsychiatry.com

Author Affiliations: King's College London, MRC Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, London, England (Waszczuk, Zavos, Eley); Department of Psychology, Goldsmiths, University of London, London, England (Gregory).

Corresponding Author: Thalia C. Eley, PhD, MRC Social, Genetic, and Developmental Psychiatry Centre, PO Box 80, Institute of Psychiatry, King's College London, De'Crespigny Park, London, SE5 8AF, England (thalia.eley@kcl.ac.uk).

The publication of the *DSM-5* has been central to the debate regarding the classification of depression and anxiety disorders.[1] Depression and anxiety commonly co-occur[2-4] and are rarely diagnosed in isolation.[2,5,6] They share multiple risk factors[7] including substantial genetic overlap.[8-12] These observations argue against diagnosis-specific etiology of depression and anxiety. However, anxiety is heterogeneous[1] and because of the age changes in internalizing disorders,[5,7,13] it remains unclear whether all anxiety types are equally associated with depression across development.[14-18] To improve diagnostic classification, the current study investigated the etiologic structure of internalizing disorder symptoms in childhood, adolescence, and early adulthood.

Most studies investigating the structure of internalizing disorders and symptoms focus on adults. Some studies provide support for a unidimensional internalizing liability factor that underpins anxiety and depression[6,19-23] in line with evidence of shared genetic effects on several different types of anxiety disorders and depression.[10,24,25] Another influential conceptualization proposes a bidimensional hierarchical model in which generalized anxiety disorder and depression form a distress factor, while the remaining anxiety disorders form a fear factor.[26-30] These 2 factors may be underpinned by separate genetic influences.[31] Importantly, fear and distress are generally highly correlated with each other, thus the 2 conceptualizations are not mutually exclusive.

To our knowledge, few studies to date have used a developmental approach to investigating the structure of internalizing disorder symptoms to test whether the structure is consistent at different developmental stages. Phenotypic studies in children and adolescents provide mixed conclusions. Some support a unidimensional internalizing factor,[32-34] others identify the distress and fear dimensions,[35,36] and 1 study found that depression and anxiety disorders generally cluster into *DSM*-related categories.[37] Twin and family studies largely provide evidence for the shared etiology of mood and anxiety disorder symptoms in young people in line with the unidimensional conceptualization.[38-43] Importantly, most of these studies encompass broad age ranges spanning childhood and adolescence, thus the associations at specific developmental stages remain unknown.

Age effects are essential to consider given that depression and anxiety disorders are characterized by different ages at onset[2,5,44] and have developmentally dynamic etiologies. Environmental influences tend to decrease, while heritability increases with age and genetic innovation and attenuation take place at multiple stages.[12,13,45-50] Furthermore, depression may differ substantially pre-adolescence and postadolescence,[51-57] with 1 study finding that only the latter shares genetic influences with anxiety disorders.[40] Thus, it is plausible that despite continuing comorbidity of internalizing problems, the genetic structure changes during development.[5]

The present analyses examined these important taxonomic issues by using a genetically informed design to investigate the structure of internalizing psychopathology cross-sectionally at multiple ages: childhood, adolescence, and early adulthood. To our knowledge, this is the first study to combine 5 waves of phenotypic and genetic data on depression symptoms and 4 anxiety subscales—generalized anxiety disorder, panic, separation anxiety, and social phobia symptoms—to address this question from a developmental perspective. The genetic structures of internalizing symptoms were investigated using 3 alternative models based on previous research: *DSM-5*–related structure and unidimensional and bidimensional (fear and distress) models. Because of the mixed findings and broad age ranges of previous research, the current study tested alternative models in an exploratory manner.

Methods

Participants

The analyses used data from 2 longitudinal twin studies: waves 1 and 2 from the Emotions, Cognitions, Heredity and Outcome Study (ECHO, child twin sample) and waves 2 through 4 from the Genesis 12-19 Study (adolescent/young adult twin and sibling sample). Full recruitment details are provided elsewhere[58,59] (eAppendix in the Supplement). The studies were given ethical approval by the research ethics committees of the Institute of Psychiatry, King's College London, South London and Maudsley NHS Trust and of Goldsmiths University, London. Written informed consent was obtained from parents of children younger than 16 years and from adolescents older than 16 years. Sample characteristics are presented in **Table 1**.

Measures

Depression

Child participants completed the Children's Depression Inventory,[62] a 27-item self-report questionnaire examining affective, cognitive, and behavioral signs of current depression. Adolescents and young adults completed the Short Mood and Feelings Questionnaire,[63] a 13-item self-report measure assessing how often depressive symptoms occurred in the previous 2 weeks. Responses were summed to give total depression scores. Both measures demonstrate good reliability and validity.[62,63]

Anxiety

Children's anxiety disorder symptoms were measured using the Screen for Child Anxiety Related Emotional Disorders.[64] Children indicated how often in the last 3 months they experienced symptoms described by 41 questionnaire items. The adolescents completed the Spence Children's Anxiety Scale,[65] a 38-item self-report questionnaire tapping common anxiety symptoms. Adults completed the Revised Symptoms of Anxiety Scale,[66] an age-appropriate version of the Revised Child Anxiety and Depression Scale,[67] consisting of 36 self-report items designed to assess *DSM-IV* anxiety and depressive disorder symptoms. Responses were summed to create 4 *DSM-IV*–related anxiety subscale scores: generalized anxiety, panic/somatic symptoms, separation anxiety, and social anxiety. All measures have sound psychometric properties.[64-67]

Table 1. Sample Characteristics and Descriptive Statistics[a]

Characteristic	ECHO Study[b]		G1219 Study		
	Wave 1 Child	Wave 2 Child	Wave 2 Adolescent	Wave 3 Adolescent	Wave 4 Young Adult
Pairs, No.[c]	300	250	1372	866	896
Pairs by sex, No. (%)					
Female	169.5 (57)	141 (56)	768 (56)	520 (60)	547 (61)
Male	130.5 (43)	109 (44)	604 (44)	346 (40)	349 (39)
Age, mean (range), y/mo	8/6 (8/2-8/11)	10/1 (9/7-10/10)	15/0 (12/0-21/0)	17/0 (14/0-23/0)	20/0 (18/0-27/0)
Zygosity, No.[d]					
MZ	100	83	350	234	230
DZ	82	69	313	207	214
DZO	117	98	334	232	232
Sib	0	0	330[2]	182	201
Depression					
No.	575	499	2630	1590	1549
Mean (SD)	10.27 (6.94)	8.22 (5.82)	8.08 (6.65)	6.25 (5.33)	6.45 (5.73)
Skew	0.91	1.06	1.35	1.14	1.26
Kurtosis	3.66	4.07	4.86	3.90	4.22
α	0.81	0.82	0.86	0.79	0.90
Generalized anxiety					
No.	578	489	2632	1555	1552
Mean (SD)	5.52 (3.51)	5.08 (3.46)	5.17 (2.98)	4.87 (2.92)	4.81 (2.97)
Skew	0.42	0.67	0.87	0.81	0.82
Kurtosis	2.71	3.12	4.12	3.82	3.73
α	0.69	0.76	0.77	0.78	0.70
Panic/somatic					
No.	578	489	2619	1565	1552
Mean (SD)	7.15 (4.53)	5.71 (3.93)	2.82 (3.26)	1.40 (2.24)	3.57 (3.61)
Skew	0.57	0.86	1.83	2.55	2.13
Kurtosis	2.82	3.89	7.48	11.53	9.83
α	0.75	0.76	0.77	0.78	0.86
Separation anxiety					
No.	578	489	2622	1568	1551
Mean (SD)	7.46 (3.53)	6.06 (2.24)	2.90 (2.50)	2.72 (1.42)	2.65 (2.91)
Skew	0.11	0.42	1.35	1.02	1.83
Kurtosis	2.40	2.84	5.68	4.76	7.73
α	0.69	0.69	0.67	0.66	0.77
Social anxiety					
No.	578	489	2625	1572	1551
Mean (SD)	6.80 (2.96)	6.27 (3.03)	5.97 (3.31)	4.37 (2.70)	10.91 (5.45)
Skew	−0.12	0.05	0.52	0.54	0.43
Kurtosis	2.68	2.74	2.95	2.85	2.89
α	0.51	0.58	0.72	0.78	0.83

Abbreviations: DZO, dizygotic (opposite-sex pairs); DZ, dizygotic (same-sex pairs); ECHO, Emotions, Cognitions, Heredity and Outcome; G1219, Genesis 12-19 Study; MZ, monozygotic; sib, siblings.

[a] Different measures were used at different points, thus the means cannot be compared across certain time points. To check for measurement effects, longitudinal correlations between anxiety subscales scores are presented in eTable 4 in the Supplement. The results suggest comparable continuity of anxiety symptom scores within and across anxiety measures. The results presented on untransformed variables for comparison with other published samples.

[b] In ECHO, data from 11 twins pairs (4%) were excluded because at least 1 twin in that pair had known neurologic or receptive language impairments, autistic spectrum disorder, or attention difficulties or because researchers observed substantial difficulty completing the tasks.

[c] Total number of twin and sibling pairs in sample at each point.

[d] Twin pair zygosity was identified in both samples using a combination of parent-rated child and adolescent questionnaires[60,61] and DNA sequencing in uncertain cases. The number of twin pairs does not add up to totals owing to a number of twin pairs of unknown zygosity (ECHO wave 1 = 1; G1219 wave 2 = 45, wave 3 = 11, and wave 4 = 19). These pairs were excluded from genetic analyses.

The internal consistencies and descriptive statistics of all measures are presented in Table 1.

Analyses

Phenotypic Analyses

Descriptive statistics were conducted using Stata (StataCorp).[68] The associations between depression and anxiety subtypes were explored using full and partial correlations. For example, to investigate the unique association between depression and generalized anxiety symptoms, the scores on all other anxiety scales were controlled. This tested associations over and above the relationships with other variables that might confound the association owing to high covariance.

Genetic Analyses

The twin design compares the similarity between monozygotic (sharing 100% of their genes) and dizygotic (sharing on average 50% of their segregating genes) twin pairs. Relative differences in within-pair correlations allow estimations of the influences of additive genetics, shared environment, and non-

shared environment. Quantitative genetic methods are described comprehensively elsewhere.[69]

Models were fitted using OpenMx[70] within R,[71] a structural equation modeling package for the analysis of genetically informative data. Sampling weights were incorporated into child analyses, although they did not influence the results in a manner that would alter interpretation.[72] The weight controls for biases due to selection criteria. Lower weights were assigned to individuals from categories overrepresented in the sample and higher weights to individuals from categories underrepresented relative to the population distribution. As is standard in model fitting analysis, variables were regressed for age and sex,[73] and any with skew greater than 1 were transformed.

Univariate genetic analyses were conducted on all variables at each wave. Owing to sample size, sex differences were only examined in G1912. Scalar sex differences that examine whether males and females showed differences in variance were tested. A scalar model was fitted in twin modeling analyses for all variables except for social phobia (for which there was no difference in variance between males and females). Quantitative sex differences were tested to see whether males and females differ in magnitude of genetic and environmental influences but such differences were not found.

Three multivariate models that test different genetic structures underpinning associations between depression and anxiety subscales were fitted. They are discussed in the following order: *DSM-5*–related, unidimensional, and bidimensional (fear and distress) structures. The first model was a correlated factors solution (**Figure**, A), which is in line with the *DSM-5* conceptualization in which each disorder is classified independently but expected to correlate with other disorders. This model includes additive genetic, shared environmental, and nonshared environmental influences on each of the scales and tests whether the correlation between them is due to correlations among the genetic and environmental factors that influence each of them. Each set of influences is allowed to correlate with one another. As such, the correlation among the variables can be mediated via genetic or environmental routes.

The second model was a 1-factor independent pathway model (Figure, B). This model reflects the unidimensional conceptualization by allowing internalizing disorder symptoms to share common genetic and environmental influences. It tests whether there is a single set of common etiologic factors that influence depression and all anxiety subscales, accounting for their correlations, in addition to variable-specific factors. The model includes 1 set of common additive genetic, shared environmental, and nonshared environmental factors that influence each of the measured variables.

The third model was a 2-factor independent pathway model (Figure, C). This model is similar to the 1-factor independent pathway model but contains a second common genetic factor loading on the anxiety symptoms hypothesized to belong to the fear factor. This model reflects the bidimensional conceptualization and tests whether there are 2 common genetic factors (distress and fear) and 1 common nonshared environmental factor that influences all variables, accounting for their correlation, in addition to variable specific factors.

Models were fitted using raw data maximum likelihood. The core fit statistic was minus twice the log likelihood of the observations. This is not an overall measure of fit but provides a relative measure of fit because differences in minus twice the log likelihood between models are distributed as χ^2. Therefore, to examine the overall fit of the genetic model, we compared the minus twice the log likelihood with that of a saturated model (one which fully describes data using the maximum number of free parameters, estimating variances, covariances, and means for the raw data to get a baseline index of fit). The fit of submodels was assessed by χ^2 difference tests, the Akaike Information Criterion (AIC), and the Bayesian Information Criterion (BIC) (AIC = χ^2 - 2df; BIC = χ^2 - *k*ln[n]), with lower χ^2 values and more negative AIC and BIC values suggesting a better fit. If the difference between the AIC of 2 models was less than 10, the more parsimonious model was selected.[74] Independent pathway models are nested in the correlated factors solution, and the 1-factor independent pathway model is nested in the 2-factor independent pathway model. Information about the precision of parameter estimates was obtained by likelihood-based confidence intervals. The analyses were repeated excluding siblings to narrow the age ranges (eTable 1 in the Supplement) and including an additional anxiety subscale: fear of physical injury (only available at the 2 adolescent time points; eTable 2 in the Supplement).

Results

The results focused on the association between depression and the different anxiety subscales. The phenotypic and genetic associations among the anxiety subscales are presented elsewhere.[72,75]

Phenotypic Results

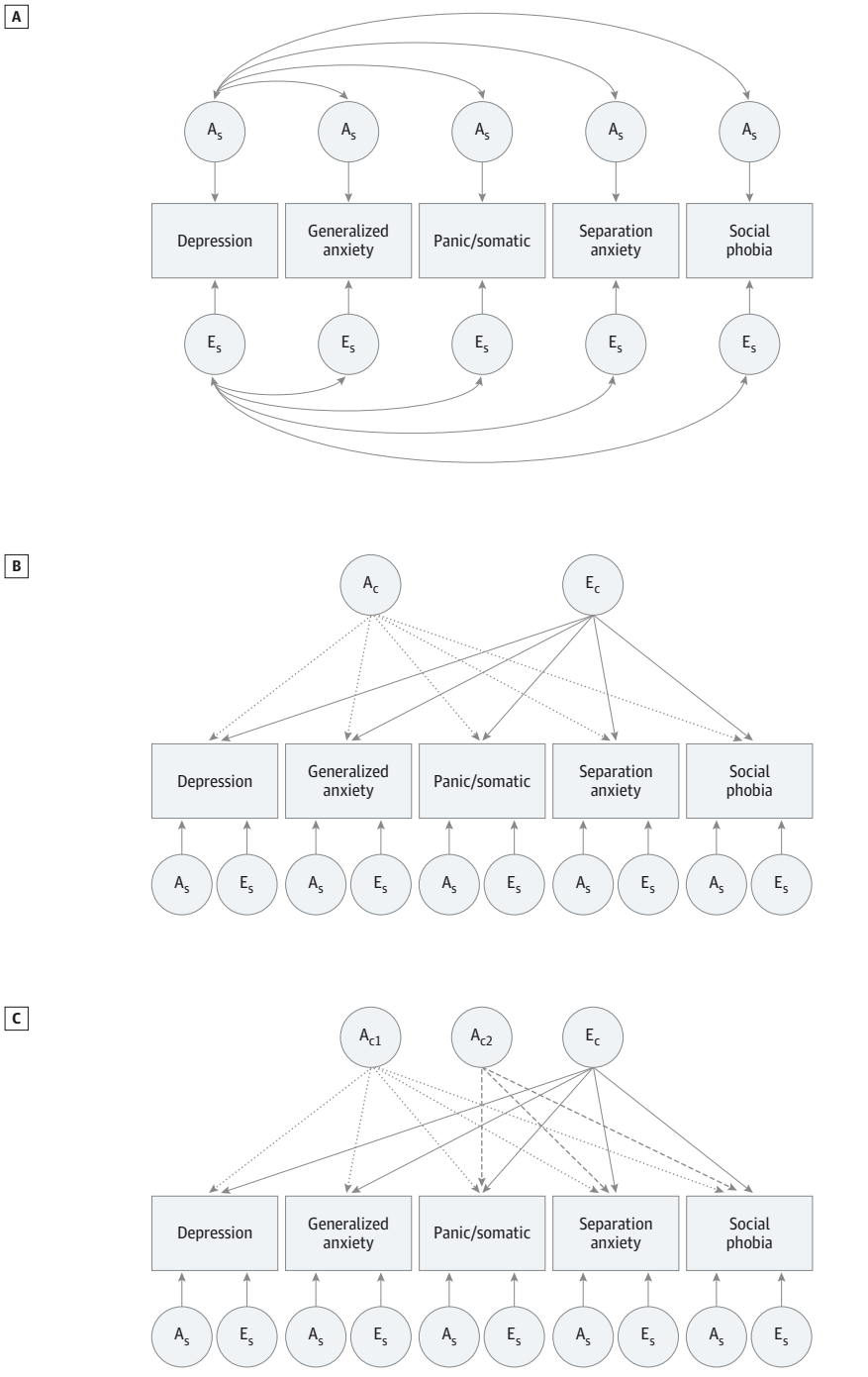
Full correlations at all ages showed that depression symptoms were significantly associated with all anxiety subscales (**Table 2**). In childhood and adolescence, depression symptoms showed significantly stronger correlations with generalized anxiety symptoms (r = 0.36 to 0.60) than with all other subscales except for panic symptoms (r = 0.28 to 0.57).

Partial correlations that controlled for all other variables within times are shown in Table 2. In childhood, when controlling for concurrent associations, depression symptoms were only significantly associated with generalized anxiety symptoms (r = 0.21 and 0.20). At 15 years, partial correlations revealed that depression symptoms were significantly associated with 3 anxiety subscales: generalized anxiety (r = 0.19), panic (r = 0.24), and social phobia (r = 0.14) symptoms. At a mean age of 17 years and in young adulthood, depression symptoms were significantly associated with all anxiety subscales even when controlling for concurrent associations.

Genetic Results

Univariate analyses revealed that genetic influences on depression and anxiety symptoms were generally small to moderate, shared environmental influences were small and non-

Figure. Multivariate Model Diagrams



The diagrams present the 3 multivariate models fitted to the data: correlated factors solution (*DSM-5* conceptualization) (A), 1-factor independent pathway model (unidimensional conceptualization) (B), and 2-factor independent pathway model (bidimensional distress and fear conceptualization) (C). The figure is for illustrative purposes only; only the genetic and nonshared environmental associations are shown. The diagram in part A illustrates only the genetic and nonshared environmental correlations between depression and anxiety subscales. A_c and A_{c1} indicate additive genetic influences acting via a common factor on all variables; A_{c2}, additive genetic influences acting via a common factor on 3 fear variables; A_s, additive genetic influences acting on a specific variable; E_c, nonshared environmental influences acting via a common factor on all variables; and E_s, nonshared environmental influences acting on a specific variable.

significant, and nonshared environmental influences were large (eTable 3 in the Supplement). Multivariate model fitting results are presented in **Table 3**. Shared environmental influences were nonsignificant and were dropped from the models without a significant deterioration of the fit in adolescence and young adulthood; fit statistics and parameter estimates are therefore presented for models with additive genetic and nonshared environmental influences.

In childhood, the most restrictive 1-factor independent pathway model was the best fitting model (**Table 4**). The common genetic factor accounted for most of the genetic influences on all anxiety subscales but did not contribute to genetic variance in depression symptoms, which instead was influenced by unique genetic influences. There were moderate to large unique nonshared environmental influences on each symptom.

Table 2. Full and Partial Correlations Between Depression and Anxiety Subscales in Childhood, Adolescence, and Early Adulthood[a]

	Childhood[b,c]		Adolescence[b,c]		Young Adulthood[b,c]
	Mean Age, y				
Correlation	8	10	15	17	20
Full correlations with depression					
Generalized anxiety	0.40 (0.33 to 0.47)	0.36 (0.31 to 0.46)	0.60 (0.58 to 0.62)	0.59 (0.56 to 0.62)	0.56 (0.53 to 0.59)
Somatic/panic	0.32 (0.25 to 0.39)	0.28 (0.20 to 0.36)	0.57 (0.54 to 0.60)	0.48 (0.44 to 0.52)	0.51 (0.47 to 0.55)
Separation anxiety	0.24 (0.16 to 0.32)	0.23 (0.15 to 0.31)	0.42 (0.39 to 0.45)	0.16 (0.11 to 0.21)	0.50 (0.46 to 0.54)
Social phobia	0.18 (0.10 to 0.26)	0.18 (0.09 to 0.26)	0.47 (0.44 to 0.50)	0.44 (0.40 to 0.48)	0.54 (0.50 to 0.57)
Partial correlations with depression[d]					
Generalized anxiety	0.21 (0.13 to .29)	0.20 (0.11 to 0.28)	0.19 (0.15 to 0.23)	0.29 (0.24 to 0.34)	0.14 (0.09 to 0.19)
Somatic/panic	0.07 (−0.01 to .15)	0.04 (−0.05 to 0.13)	0.24 (0.20 to 0.28)	0.17 (0.12 to 0.22)	0.15 (0.10 to 0.20)
Separation anxiety	−0.03 (−0.11 to 0.05)	0.04 (−0.05 to 0.13)	−0.02 (−0.06 to 0.02)	−0.14 (−0.19 to −0.09)	0.06 (0.01 to 0.11)
Social phobia	−0.05 (−0.13 to 0.03)	−0.02 (−0.11 to 0.07)	0.14 (0.10 to 0.18)	0.16 (0.11 to 0.21)	0.19 (0.14 to 0.24)

[a] Results presented on untransformed variables for comparison with other published samples. The correlations between anxiety disorder subscales are discussed elsewhere.[72,75] The additional analyses inclusive of fear of physical injury symptoms (at mean ages 15 and 17 years) are presented in eTable 2 in the Supplement.

[b] The childhood sample comes from the Emotions, Cognitions, Heredity and Outcome Study; the adolescent sample comes from waves 2 and 3 and the young adult sample comes from wave 4 of the Genesis 12-19 Study.

[c] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations (in bold). Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects the larger sample size of the Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

[d] Partial correlations controlled for all other anxiety variables within time.

In adolescence, the least restrictive model, the correlated factors solution, showed the best fit to the data in line with *DSM-5* conceptualization (**Table 5**). Genetic correlations were mostly large. Depression symptoms generally had higher genetic correlations with generalized anxiety (r = 0.71 and 0.74), panic (r = 0.78 and 0.61), and social phobia (r = 0.66 and 0.53) than with separation anxiety (r = 0.52 and 0.15) symptoms. Nonshared environmental correlations were generally moderate. Genetic influences explained a substantial proportion of the phenotypic correlation between depression and anxiety subscales (36% to 100%).

In young adulthood, a 2-factor independent pathway model showed the best fit to the data in line with a bidimensional conceptualization (**Table 6**). The first common genetic factor loaded significantly on all variables and accounted for most of the genetic variance. The second common genetic factor, specified to load on the fear variables, showed small but significant contributions to panic, separation anxiety, and social phobia symptoms. In addition, depression and generalized anxiety symptoms had significant unique genetic influences. The common nonshared environmental factor loaded significantly on all variables but there were also significant unique nonshared environmental influences on each variable.

Discussion

To our knowledge, this study is the first to investigate the phenotypic and genetic structure of internalizing disorder symptoms at 3 developmental stages. The results provide preliminary evidence for developmental differences in the associations between depression and multiple anxiety disorder symptoms, advancing the search for an evidence-based conceptualization of internalizing disorders in diagnostic manuals.

We observed different etiologic structures of internalizing disorder symptoms at 3 developmental phases, with common genetic vulnerability across depression and anxiety disorder symptoms only emerging in adolescence. Specifically, in childhood, when controlling for concurrent associations, only the generalized anxiety disorder symptoms were associated with depression. Furthermore, childhood depression was influenced by separate genetic factors from the anxiety subscales. In adolescence, comorbidity began to increase—partial correlations revealed that at 15 years of age, depression was associated with 3 anxiety disorder subscales: generalized anxiety disorder, panic, and social phobia symptoms. At this developmental stage, the etiologic structure reflected the *DSM-5* conceptualization of distinct but correlated disorders in contrast to previous studies that found support for unidimensional or bidimensional latent factor structures in young people.[32-36] These age differences may be explained by anxiety emerging in childhood, while depression peaks in adolescence,[2,36]and are in agreement with previous studies finding that depression pre-adolescence and post-adolescence may differ substantially,[51-57] which could be explained by significant new genetic influences coming online after puberty.[12,13,45,46,48]

In young adulthood, these associations broadened even further, and depression was significantly correlated with all anxiety disorder symptom scales. Genetic analyses provided support for both unidimensional[19-22] and bidimensional[26-30] conceptualizations of internalizing psychopathology. The 2 genetic factors representing distress and fear emerged, although the genetic fear factor had a relatively small influence on the fear symptoms. The current results add to a

Table 3. Multivariate Model Fit Statistics in Childhood, Adolescence, and Early Adulthood[a]

Period[b]	−2LL	*df*	Comparison With Saturated Model[c]			Comparison With Correlated Factors Solution			Comparison With 2-Factor Independent Pathway Model			AIC	BIC (Size-Adjusted)
			χ^2	Δ *df*	*P* Value	χ^2	Δ *df*	*P* Value	χ^2	Δ *df*	*P* Value		
Childhood, 8 y													
Saturated model	12 970.90	2747										7476.91	13 299.68
Correlated factors solution	13 084.65	2827	113.75	80	.01							7430.65	13 211.10
2-Factor independent pathway model	13 092.67	2839	121.77	92	.02	8.02	12	.78				7414.67	13 188.77
1-Factor independent pathway model[d]	13 094.21	2842	123.31	95	.03	9.56	15	.85	1.54	3	.67	7410.21	13 182.73
Childhood, 10 y													
Saturated model	6919.34	2091										2737.34	7217.04
Correlated factors solution	7047.12	2171	127.78	80	<.01							2705.12	7161.62
2-Factor independent pathway model	7060.67	2183	141.33	92	<.01	13.55	12	.33				2694.67	7147.69
1-Factor independent pathway model[d]	7068.86	2186	149.52	95	<.01	21.74	15	.11	8.19	3	.04	2696.86	7144.15
Adolescence, 15 y													
Saturated model	34 539.26	12183										10 173.26	37 116.75
Correlated factors solution[d]	35 207.38	12664	668.12	481	<.01							9879.38	35 400.69
2-Factor independent pathway model	35 245.11	12671	705.85	488	<.01	37.73	7	<.01				9903.11	35 403.73
1-Factor independent pathway model	35 297.10	12674	757.83	491	<.01	89.72	10	<.01	51.99	3	<.01	9949.10	35 440.84
Adolescence, 17 y													
Saturated model	19 082.97	7202										4678.97	21 660.45
Correlated factors solution[d]	19 758.02	7683	675.05	481	<.01							4392.02	19 951.33
2-Factor independent pathway model	19 823.33	7690	740.36	488	<.01	65.31	7	<.01				4443.33	19 981.94
1-Factor independent pathway model	19 844.34	7693	761.37	491	<.01	86.32	10	<.01	21.01	3	<.01	4458.34	19 988.08
Young adulthood, 20 y													
Saturated model	22 999.04	7065										8869.04	25576.53
Correlated factors solution	23 556.80	7546	557.76	481	<.01							8464.80	23 750.11
2-Factor independent pathway model[d]	23 566.13	7553	567.09	488	.01	9.33	7	.23				8460.13	23 724.74
1-Factor independent pathway model	23 587.09	7556	588.05	491	.01	30.29	10	<.01	20.96	3	<.01	8475.09	23 730.83

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; −2LL, minus twice the log likelihood.

[a] Models containing additive genetic and nonshared environmental influences are presented for the adolescent and young adult samples, as shared environmental influences were not significant (eTable 3 in the Supplement) and were dropped from the multivariate models without a significant deterioration of the fit (eTable 5 in the Supplement). The analyses were repeated excluding siblings to narrow the age ranges (at mean ages 15, 17, and 20 years; eTable 1 in the Supplement) and including an additional anxiety subscale: fear of physical injury (at mean ages 15 and 17 years; eTable 2 in the Supplement). The pattern of effects and the best fitting models remained the same at each time point.

[b] The childhood sample comes from the Emotions, Cognitions, Heredity and Outcome Study; the adolescence sample comes from waves 2 and 3 and the young adult sample comes from wave 4 from the Genesis 12-19 Study. Mean ages are provided in the headers.

[c] The multivariate genetic models were significantly different from the saturated model indicating poor fit; however, this is common in studies with large sample sizes because minimal variance differences between groups can be highly statistically significant.

[d] The best fitting model was selected based on the principle of parsimony and lowest AIC and BIC value. A difference in AIC between 2 models of 2 or less provides equivalent support for both models (in which case the most parsimonious model should be chosen), a difference of 3 indicates that the lower AIC model has considerably more support, and a difference of more than 10 indicates that the lower AIC model is a substantially better fit compared with the higher AIC model.[74] At age 10 years, the difference between AIC for 1- and 2-factor independent pathway models was 2.19, thus the 1-factor independent pathway model was selected because it is more parsimonious.

debate as to whether generalized anxiety disorder ought to be classified together with depression,[14-17] and they suggest that at most ages, generalized anxiety disorder symptoms are no more closely related to depression than other anxiety subtypes. The exception is childhood, where the generalized anxiety disorder symptom subscale was the only one associated with depression, although this association was not underpinned by shared genes.

While genetic influences accounted for comorbidity, in agreement with the generalist genes hypothesis,[76] the nonshared environment was largely symptom specific across development, accounting for most of the unique variance that makes each disorder symptom a discrete condition. These results carry implications for the molecular genetic studies of depression and anxiety, which in turn may inform clinical interventions.[77-79] The results provide preliminary support for

Table 4. Model Fitting Results For 1-Factor Independent Pathway Model Results in the Child Sample[a,b]

	Common Factors			Specific Influences		
Subscale	A_c	C_c	E_c	A_s	C_s	E_s
Depression[c]						
Age 8 y	0.00 (0.00-0.19)	0.15 (0.04-0.33)	0.18 (0.09-0.30)	0.17 (0.00-0.35)	0.00 (0.00-0.22)	0.49 (0.37-0.65)
Age 10 y	0.02 (0.00-0.42)	0.15 (0.00-0.52)	0.04 (0.00-0.12)	0.00 (0.00-0.30)	0.21 (0.00-0.37)	0.58 (0.45-0.69)
Generalized anxiety						
Age 8 y	0.13 (0.01-0.30)	0.03 (0.00-0.15)	0.35 (0.22-0.49)	0.01 (0.00-0.12)	0.00 (0.00-0.07)	0.47 (0.36-0.56)
Age 10 y	0.06 (0.00-0.44)	0.14 (0.00-0.29)	0.35 (0.20-0.77)	0.01 (0.00-0.16)	0.00 (0.00-0.08)	0.43 (0.12-0.54)
Panic/somatic						
Age 8 y	0.16 (0.00-0.40)	0.07 (0.00-0.23)	0.47 (0.31-0.63)	0.04 (0.00-0.14)	0.00 (0.00-0.08)	0.25 (0.15-0.35)
Age 10 y	0.03 (0.00-0.45)	0.11 (0.00-0.31)	0.50 (0.19-0.72)	0.08 (0.00-0.24)	0.00 (0.00-0.17)	0.27 (0.11-0.54)
Separation anxiety						
Age 8 y	0.27 (0.10-0.42)	0.00 (0.00-.010)	0.26 (0.15-0.40)	0.00 (0.00-0.11)	0.00 (0.00-0.05)	0.46 (0.36-0.55)
Age 10 y	0.08 (0.00-0.55)	0.08 (0.00-0.28)	0.22 (0.03-0.34)	0.14 (0.00-0.27)	0.00 (0.00-0.14)	0.48 (0.36-0.63)
Social phobia						
Age 8 y	0.12 (0.00-0.24)	0.00 (0.00-0.08)	0.28 (0.17-0.46)	0.00 (0.00-0.07)	0.00 (0.00-0.04)	0.59 (0.49-0.68)
Age 10 y	0.38 (0.00-0.53)	0.01 (0.00-0.27)	0.21 (0.09-0.40)	0.00 (0.00-0.42)	0.00 (0.00-0.25)	0.40 (0.27-0.54)

Abbreviations: A_c, additive genetic influences acting via a common factor on all variables; A_s, additive genetic influences acting on a specific variable; C_c, shared environmental influences acting via a common factor on all variables; C_s, shared environmental influences acting on a specific variable; E_c, nonshared environmental influences acting via a common factor on all variables; E_s, nonshared environmental influences acting on a specific variable.

[a] In the child sample, shared environment was modeled and submodel comparisons revealed that shared environment could be dropped from the model without a significant deterioration of the fit. However, large sample sizes are required to reliably model effects of shared environment and we chose not to drop the shared environment parameter in the child sample to avoid artificially inflating additive genetics estimates.

[b] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations. Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects the larger sample size of the Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

[c] Depression at time 2 in the child sample (Emotions, Cognitions, Heredity and Outcome Study) showed a different pattern of parameter estimates than other variables, being influenced by moderate shared environmental factors with no genetic influence. This is due to a low power to distinguish additive genetics and shared environment in the Emotions, Cognitions, Heredity and Outcome Study sample.

Table 5. Model Fitting Results For Correlated Factor Solution Results in Adolescents[a,b,c]

Variable	Generalized Anxiety	Panic	Separation Anxiety	Social Phobia
Genetic correlations with depression				
15 y	0.71 (0.63 to 0.78)	0.78 (0.70 to 0.86)	0.52 (0.43 to 0.61)	0.66 (0.57 to 0.75)
17 y	0.74 (0.63 to 0.85)	0.61 (0.48 to 0.73)	0.15 (−0.01 to 0.32)	0.53 (0.38 to 0.66)
Nonshared environmental correlations with depression				
15 y	0.40 (0.33 to 0.47)	0.34 (0.27 to 0.41)	0.34 (0.27 to 0.42)	0.30 (0.22 to 0.38)
17 y	0.41 (0.32 to 0.50)	0.36 (0.26 to 0.45)	0.00 (−0.11 to 0.11)	0.36 (0.27 to 0.45)
Proportion of phenotypic correlation with depression due to additive genetic influences				
15 y	0.62 (0.53 to 0.71)	0.66 (0.57 to 0.74)	0.58 (0.47 to 0.69)	0.66 (0.56 to 0.76)
17 y	0.58 (0.45 to 0.69)	0.57 (0.41 to 0.71)	1.00[d]	0.50 (0.34 to 0.64)
Proportion of phenotypic correlation with depression due to nonshared environmental influences				
15 y	0.38 (0.29 to 0.47)	0.34 (0.26 to 0.43)	0.42 (0.31 to 0.53)	0.34 (0.24 to 0.44)
17 y	0.42 (0.31 to 0.55)	0.43 (0.29 to 0.58)	0.00[d]	0.50 (0.36 to 0.66)

[a] Additive genetics/nonshared environment models are presented for the adolescent sample because shared environment influences were not significant (eTable 3 in the Supplement) and were dropped from the multivariate models without a significant deterioration of the fit (eTable 5 in the Supplement). The Akaike Information Criterion values suggest that dropping shared environment led to improvement of the model fit at these 3 waves.

[b] Additional analyses inclusive of fear of physical injury symptoms (at mean ages 15 and 17) are presented in eTable 2 in the Supplement.

[c] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations. Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects larger sample size of Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

[d] 95% CIs not available due to zero environmental correlation between depression and separation anxiety symptoms at age 17 years.

Table 6. Model Fitting Results For 2-Factor Independent Pathway Model Results in Young Adults[a,b]

	Common Factors			Specific Influences	
Subscale	A_{c1}	A_{c2}	E_c	A_s	E_s
Depression	0.26 (0.17-0.35)		0.19 (0.12-0.27)	0.15 (0.08-0.22)	0.41 (0.34-0.48)
Generalized anxiety	0.33 (0.24-0.43)		0.34 (0.25-0.44)	0.07 (0.02-0.12)	0.26 (0.20-0.32)
Panic/somatic	0.26 (0.17-0.35)	0.02 (0.01-0.08)	0.29 (0.20-0.39)	0.05 (0.00-0.12)	0.37 (0.31-0.44)
Separation anxiety	0.27 (0.18-0.37)	0.04 (0.01-0.14)	0.27 (0.19-0.37)	0.05 (0.00-0.13)	0.36 (0.29-0.43)
Social phobia	0.40 (0.30-0.49)	0.07 (0.01-0.12)	0.26 (0.18-0.34)	0.00 (0.00-0.00)	0.27 (0.22-0.33)

Abbreviations: A_{c1}, additive genetic influences acting via a common factor on all variables; A_{c2}, additive genetic influences acting via a common factor on 3 fear variables; A_s, additive genetic influences acting on a specific variable; E_c, nonshared environmental influences acting via a common factor on all variables; E_s, nonshared environmental influences acting on a specific variable.

[a] Additive genetics/nonshared environment models are presented for the young adult sample because shared environment influences were not significant (eTable 3 in the Supplement) and were dropped from the multivariate models without a significant deterioration of the fit (eTable 5 in the Supplement). The Akaike Information Criterion values suggest that dropping shared environment led to improvement of the model fit at these 3 waves.

[b] 95% CIs are presented in parentheses; 95% CIs not inclusive of zeroes indicate significant correlations. Nonoverlapping 95% CIs mean there is a significant difference between the values. The difference in 95% CI width between the Emotions, Cognitions, Heredity and Outcome Study and Genesis 12-19 Study time points reflects larger sample size of Genesis 12-19 Study, which results in greater power to estimate the parameters precisely.

broadening phenotypic definitions in linkage or association studies, as including adult cases with a variety of internalizing disorders underpinned by an overarching genetic internalizing factor would lead to increasing power to detect shared susceptibility loci.[80] Conversely, the difference in the genetic results pre-adolescence and postadolescence also provides a preliminary argument for narrowing the phenotypic definitions by age.[81]

A key clinical implication of our findings was the support for transdiagnostic treatment approaches for anxiety and depression disorders, which are designed to target common elements of several disorders in 1 protocol.[82-87] The developmental pattern of the data suggests that while disorder-specific treatment may be more appropriate for pediatric patients, treatment focused on a range of symptoms common to internalizing disorders may be more appropriate for older patients. The evidence for a shared genetic etiologic factor is in agreement with the findings that internalizing disorders respond to similar interventions and therapies.[23,86-91]

The genetically informative, representative samples and multiple time points were strengths of the current study. However, a number of limitations are noteworthy. First, the child sample was smaller than the adolescent/adult sample. Although considered large for phenotypic analyses, the child sample had reduced power to examine sex differences or shared environmental influences, and parameter estimates had large confidence intervals. Replication in larger pediatric twin samples is essential. However, because of the internal replication of results across the 2 time points, interpretations seem broadly applicable for childhood. Second, the inclusion of siblings in the Genesis 12-19 Study meant there were large age ranges in adolescence and early adulthood. However, 72% of the participants were twins, and additional analyses excluding siblings suggest that the results are applicable to tighter age ranges. Third, to inform understanding of comorbidity of internalizing disorders in clinical settings, the results should be replicated in clinical samples with comorbid diagnoses and using lifetime diagnostic interviews. However, internalizing symptoms are important markers of psychopathology[92-94] and because common mental disorders are quantitative traits,[95] there is evidence that differently defined internalizing problems have the same etiology.[8,96,97] Fourth, our study included self-report measures, allowing comparisons across waves. While studies have shown that young children can accurately report on their own internalizing symptoms,[98,99] including parent-report measures at these waves may have strengthened our findings. Last, there are limitations inherent to the twin design, discussed comprehensively elsewhere.[100] These have minimal and contrasting effects on parameter estimates that should therefore be taken as indicative rather than absolute.

Conclusions

Our results suggest that the phenotypic and genetic structure of internalizing disorder symptoms may differ across development. Depression and anxiety seem to be somewhat distinct in childhood but become more associated and share most of their genetic etiology from adolescence, with an overarching internalizing genetic factor emerging in early adulthood. The results have multiple implications for further research, taxonomy, and clinical practice. They affirm the need to continue examining developmental differences in the etiology of mood and anxiety disorders to ensure that the diagnostic conceptualization of psychopathology is age appropriate.

ARTICLE INFORMATION

Submitted for Publication: November 25, 2013; final revision received February 21, 2014; accepted March 24, 2014.

Published Online: June 11, 2014. doi:10.1001/jamapsychiatry.2014.655.

Author Contributions: Ms Waszczuk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ms Waszczuk and Dr Zavos were the joint lead authors.
Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: Waszczuk, Zavos, Eley.
Drafting of the manuscript: Waszczuk.
Critical revision of the manuscript for important intellectual content: Zavos, Gregory, Eley.
Statistical analysis: Waszczuk, Zavos.
Obtained funding: Gregory, Eley.
Study supervision: Zavos, Eley.

Conflict of Interest Disclosures: None reported.

Funding/Support: Both the Emotions, Cognitions, Heredity and Outcome and Genesis 12-19 studies were supported by a Medical Research Council Training Fellowship and a Career Development Award given to Prof Eley. Waves 1 through 3 of the Genesis 12-19 Study were also funded by the W. T. Grant Foundation, the University of London Central Research fund, and wave 4 was supported by the Economic and Social Research Council (RES-000-22-2206), the Institute of Social Psychiatry, and a Leverhulme Research Fellowship awarded to Dr Gregory. Ms Waszczuk was supported by a PhD studentship awarded by the Alexander von Humboldt Foundation. This study presents independent research partly funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

Role of the Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Additional Contributions: We thank the families for their participation as well as numerous staff and students from the Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, London and Goldsmiths, University of London.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013.

2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication [published correction appears in *Arch Gen Psychiatry*. 2005;62(7):709]. *Arch Gen Psychiatry*. 2005;62(6):617-627.

3. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry*. 1999;40(1):57-87.

4. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry*. 2003;60(8):837-844.

5. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents. *Psychiatr Clin North Am*. 2009;32(3):483-524.

6. Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R. Juvenile mental health histories of adults with anxiety disorders. *Am J Psychiatry*. 2007;164(2):301-308.

7. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. *Depress Anxiety*. 2001;14(2):67-78.

8. Kendler KS, Heath AC, Martin NG, Eaves LJ. Symptoms of anxiety and symptoms of depression. *Arch Gen Psychiatry*. 1987;44(5):451-457.

9. Eley TC, Stevenson J. Using genetic analyses to clarify the distinction between depressive and anxious symptoms in children. *J Abnorm Child Psychol*. 1999;27(2):105-114.

10. Mosing MA, Gordon SD, Medland SE, et al. Genetic and environmental influences on the co-morbidity between depression, panic disorder, agoraphobia, and social phobia: a twin study. *Depress Anxiety*. 2009;26(11):1004-1011.

11. Thapar A, McGuffin P. Anxiety and depressive symptoms in childhood. *J Child Psychol Psychiatry*. 1997;38(6):651-656.

12. Zavos HM, Rijsdijk FV, Eley TC. A longitudinal, genetically informative, study of associations between anxiety sensitivity, anxiety and depression. *Behav Genet*. 2012;42(4):592-602.

13. Bergen SE, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Res Hum Genet*. 2007;10(3):423-433.

14. Mennin DS, Heimberg RG, Fresco DM, Ritter MR. Is generalized anxiety disorder an anxiety or mood disorder? considering multiple factors as we ponder the fate of GAD. *Depress Anxiety*. 2008;25(4):289-299.

15. Hettema JM. The nosologic relationship between generalized anxiety disorder and major depression. *Depress Anxiety*. 2008;25(4):300-316.

16. Moffitt TE, Harrington H, Caspi A, et al. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Arch Gen Psychiatry*. 2007;64(6):651-660.

17. Goldberg D. Towards *DSM-V*: the relationship between generalized anxiety disorder and major depressive episode. *Psychol Med*. 2008;38(11):1671-1675.

18. Beesdo K, Pine DS, Lieb R, Wittchen HU. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. *Arch Gen Psychiatry*. 2010;67(1):47-57.

19. Fergusson DM, Horwood LJ, Boden JM. Structure of internalising symptoms in early adulthood. *Br J Psychiatry*. 2006;189(6):540-546.

20. Seeley JR, Kosty DB, Farmer RF, Lewinsohn PM. The modeling of internalizing disorders on the basis of patterns of lifetime comorbidity. *J Abnorm Psychol*. 2011;120(2):308-321.

21. Krueger RF, Caspi A, Moffitt TE, Silva PA. The structure and stability of common mental disorders (*DSM-III-R*): a longitudinal-epidemiological study. *J Abnorm Psychol*. 1998;107(2):216-227.

22. Eaton NR, Krueger RF, Oltmanns TF. Aging and the structure and long-term stability of the internalizing spectrum of personality and psychopathology. *Psychol Aging*. 2011;26(4):987-993.

23. Goldberg DP, Krueger RF, Andrews G, Hobbs MJ. Emotional disorders: cluster 4 of the proposed meta-structure for *DSM-V* and *ICD-11*. *Psychol Med*. 2009;39(12):2043-2059.

24. Kendler KS, Aggen SH, Knudsen GP, Røysamb E, Neale MC, Reichborn-Kjennerud T. The structure of genetic and environmental risk factors for syndromal and subsyndromal common *DSM-IV* axis I and all axis II disorders. *Am J Psychiatry*. 2011;168(1):29-39.

25. Goes FS, McCusker MG, Bienvenu OJ, et al; National Institute of Mental Health Genetics Initiative Bipolar Disorder Consortium. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. *Psychol Med*. 2012;42(7):1449-1459.

26. Sellbom M, Ben-Porath YS, Bagby RM. On the hierarchical structure of mood and anxiety disorders: confirmatory evidence and elaboration of a model of temperament markers. *J Abnorm Psychol*. 2008;117(3):576-590.

27. Watson D. Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. *J Abnorm Psychol*. 2005;114(4):522-536.

28. Eaton NR, Krueger RF, Markon KE, et al. The structure and predictive validity of the internalizing disorders. *J Abnorm Psychol*. 2013;122(1):86-92.

29. Vollebergh WA, Iedema J, Bijl RV, de Graaf R, Smit F, Ormel J. The structure and stability of common mental disorders: the NEMESIS Study. *Arch Gen Psychiatry*. 2001;58(6):597-603.

30. Slade T, Watson D. The structure of common *DSM-IV* and *ICD-10* mental disorders in the Australian general population. *Psychol Med*. 2006;36(11):1593-1600.

31. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry*. 2003;60(9):929-937.

32. Gomez R, Vance A, Gomez RM. The factor structure of anxiety and depressive disorders in a sample of clinic-referred adolescents. *J Abnorm Child Psychol*. 2014;42(2):321-332.

33. Trosper SE, Whitton SW, Brown TA, Pincus DB. Understanding the latent structure of the emotional disorders in children and adolescents. *J Abnorm Child Psychol*. 2012;40(4):621-632.

34. Krueger RF, Finger MS. Using item response theory to understand comorbidity among anxiety and unipolar mood disorders. *Psychol Assess*. 2001;13(1):140-151.

35. Lahey BB, Rathouz PJ, Van Hulle C, et al. Testing structural models of *DSM-IV* symptoms of common forms of child and adolescent psychopathology. *J Abnorm Child Psychol*. 2008;36(2):187-206.

36. Lahey BB, Applegate B, Waldman ID, Loft JD, Hankin BL, Rick J. The structure of child and adolescent psychopathology. *J Abnorm Psychol*. 2004;113(3):358-385.

37. Higa-McMillan CK, Smith RL, Chorpita BF, Hayashi K. Common and unique factors associated with *DSM-IV-TR* internalizing disorders in children. *J Abnorm Child Psychol*. 2008;36(8):1279-1288.

38. Lahey BB, Van Hulle CA, Singh AL, Waldman ID, Rathouz PJ. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Arch Gen Psychiatry*. 2011;68(2):181-189.

39. Cosgrove VE, Rhee SH, Gelhorn HL, et al. Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. *J Abnorm Child Psychol*. 2011;39(1):109-123.

40. Silberg JL, Rutter M, Eaves L. Genetic and environmental influences on the temporal association between earlier anxiety and later depression in girls [erratum appears in *Biol Psychiatry*. 2001;50(5):393]. *Biol Psychiatry*. 2001; 49(12):1040-1049.

41. Lieb R, Isensee B, Höfler M, Pfister H, Wittchen H-U. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Arch Gen Psychiatry*. 2002;59(4):365-374.

42. Hudson JI, Mangweth B, Pope HG Jr, et al. Family study of affective spectrum disorder. *Arch Gen Psychiatry*. 2003;60(2):170-177.

43. Starr L, Conway C, Hammen C, Brennan P. Transdiagnostic and disorder-specific models of intergenerational transmission of internalizing pathology. *Psychol Med*. 2014;44(1):161-172.

44. Wittchen HU, Kessler RC, Pfister H, Lieb M. Why do people with anxiety disorders become depressed? a prospective-longitudinal community study. *Acta Psychiatr Scand Suppl*. 2000;102(406): 14-23.

45. Kendler KS, Gardner CO, Lichtenstein P. A developmental twin study of symptoms of anxiety and depression. *Psychol Med*. 2008;38(11):1567-1575.

46. Scourfield J, Rice F, Thapar A, Harold GT, Martin N, McGuffin P. Depressive symptoms in children and adolescents. *J Child Psychol Psychiatry*. 2003;44(7):968-976.

47. Rice F, Harold GT, Thapar A. Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry*. 2002;43 (8):1039-1051.

48. Kendler KS, Gardner CO, Annas P, Neale MC, Eaves LJ, Lichtenstein P. A longitudinal twin study of fears from middle childhood to early adulthood: evidence for a developmentally dynamic genome. *Arch Gen Psychiatry*. 2008;65(4):421-429.

49. Franić S, Middeldorp CM, Dolan CV, Ligthart L, Boomsma DI. Childhood and adolescent anxiety and depression: beyond heritability. *J Am Acad Child Adolesc Psychiatry*. 2010;49(8):820-829.

50. Lau JYF, Eley TC. Changes in genetic and environmental influences on depressive symptoms across adolescence and young adulthood. *Br J Psychiatry*. 2006;189:422-427.

51. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry*. 2006;47(3-4):276-295.

52. Harrington R, Fudge H, Rutter M, Pickles A, Hill J. Adult outcomes of childhood and adolescent depression, I: psychiatric status. *Arch Gen Psychiatry*. 1990;47(5):465-473.

53. Weissman MM, Wolk S, Wickramaratne P, et al. Children with prepubertal-onset major depressive disorder and anxiety grown up. *Arch Gen Psychiatry*. 1999;56(9):794-801.

54. Harrington R, Rutter M, Fombonne E. Developmental pathways in depression. *Dev Psychopathol*. 1996;8:601-616.

55. Kaufman J, Martin A, King RA, Charney D. Are child-, adolescent-, and adult-onset depression one and the same disorder? *Biol Psychiatry*. 2001;49 (12):980-1001.

56. Jaffee SR, Moffitt TE, Caspi A, Fombonne E, Poulton R, Martin J. Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Arch Gen Psychiatry*. 2002;59(3): 215-222.

57. Rice F, Harold G, Thapar A. The genetic aetiology of childhood depression: a review. *J Child Psychol Psychiatry*. 2002;43(1):65-79.

58. Eley TC, Gregory AM, Clark DM, Ehlers A. Feeling anxious: a twin study of panic/somatic ratings, anxiety sensitivity and heartbeat perception in children. *J Child Psychol Psychiatry*. 2007;48(12):1184-1191.

59. McAdams TA, Gregory AM, Rowe R, et al. The Genesis 12-19 (G1219) Study: a twin and sibling study of gene-environment interplay and adolescent development in the UK. *Twin Res Hum Genet*. 2013;16(1):134-143.

60. Price TS, Freeman B, Craig I, Petrill SA, Ebersole L, Plomin R. Infant zygosity can be assigned by parental report questionnaire data. *Twin Res*. 2000;3(3):129-133.

61. Cohen DJ, Dibble E, Grawe JM, Pollin W. Reliably separating identical from fraternal twins. *Arch Gen Psychiatry*. 1975;32(11):1371-1375.

62. Kovacs M. The Children's Depression, Inventory (CDI). *Psychopharmacol Bull*. 1985;21(4): 995-998.

63. Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. The development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *Int J Method Psych*. 1995;5:1-12.

64. Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): a replication study. *J Am Acad Child Adolesc Psychiatry*. 1999;38(10):1230-1236.

65. Spence SH. A measure of anxiety symptoms among children. *Behav Res Ther*. 1998;36(5): 545-566.

66. Gregory AM, Buysse DJ, Willis TA, et al. Associations between sleep quality and anxiety and depression symptoms in a sample of young adult twins and siblings. *J Psychosom Res*. 2011;71(4): 250-255.

67. Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of *DSM-IV* anxiety and depression in children. *Behav Res Ther*. 2000;38(8):835-855.

68. StataCorp. *Stata Statistical Software: Release 10*. College Station, TX: StataCorp LP; 2007.

69. Rijsdijk FV, Sham PC. Analytic approaches to twin data using structural equation models. *Brief Bioinform*. 2002;3(2):119-133.

70. Boker S, Neale M, Maes H, et al. OpenMx: an open source extended structural equation modeling framework. *Psychometrika*. 2011;76(2): 306-317.

71. TeamRDC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2010.

72. Lau JYF, Gregory AM, Goldwin MA, Pine DS, Eley TC. Assessing gene-environment interactions on anxiety symptom subtypes across childhood and adolescence. *Dev Psychopathol*. 2007;19(4): 1129-1146.

73. McGue M, Bouchard TJ Jr. Adjustment of twin data for the effects of age and sex. *Behav Genet*. 1984;14(4):325-343.

74. Wagenmakers E-J, Farrell S. AIC model selection using Akaike weights. *Psychon Bull Rev*. 2004;11(1): 192-196.

75. Waszczuk MA, Zavos HM, Eley TC. Genetic and environmental influences on relationship between anxiety sensitivity and anxiety subscales in children. *J Anxiety Disord*. 2013;27(5):475-484.

76. Eley TC. General genes: A new theme in developmental psychopathology. *Curr Dir Psychol*. 1997;6:90-95.

77. Lester KJ, Eley TC. Therapygenetics: using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biol Mood Anxiety Disord*. 2013;3(1):4.

78. Eley TC, Hudson JL, Creswell C, et al. Therapygenetics: the 5HTTLPR and response to psychological therapy. *Mol Psychiatry*. 2012;17(3): 236-237.

79. Keers R, Aitchison KJ. Pharmacogenetics of antidepressant response. *Expert Rev Neurother*. 2011;11(1):101-125.

80. O'Reilly PF, Hoggart CJ, Pomyen Y, et al. MultiPhen: joint model of multiple phenotypes can increase discovery in GWAS. *PLoS One*. 2012;7(5): e34861.

81. Zaitlen N, Lindström S, Pasaniuc B, et al. Informed conditioning on clinical covariates increases power in case-control association studies. *PLoS Genet*. 2012;8(11):e1003032.

82. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. *Behav Ther*. 2004;35(2):205-230. doi:10.1016/S0005-7894(04)80036-4.

83. Craske MG, Rose RD, Lang A, et al. Computer-assisted delivery of cognitive behavioral therapy for anxiety disorders in primary-care settings. *Depress Anxiety*. 2009;26(3):235-242.

84. Wilamowska ZA, Thompson-Hollands J, Fairholme CP, Ellard KK, Farchione TJ, Barlow DH. Conceptual background, development, and preliminary data from the unified protocol for transdiagnostic treatment of emotional disorders. *Depress Anxiety*. 2010;27(10):882-890.

85. Titov N, Dear BF, Schwencke G, et al. Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. *Behav Res Ther*. 2011;49(8):441-452.

86. McEvoy PM, Nathan P, Norton PJ. Efficacy of transdiagnostic treatments: a review of published outcome studies and future research directions. *J Cogn Psychother*. 2009;23(1):20-33.

87. Clark DA, Taylor S. The transdiagnostic perspective on cognitive-behavioral therapy for anxiety and depression: new wine for old wineskins? *J Cogn Psychother*. 2009;23(1):60-66.

88. Brown TA, Antony MM, Barlow DH. Diagnostic comorbidity in panic disorder. *J Consult Clin Psychol*. 1995;63(3):408-418.

89. Kendall PC, Brady EU, Verduin TL. Comorbidity in childhood anxiety disorders and treatment outcome. *J Am Acad Child Adolesc Psychiatry*. 2001; 40(7):787-794.

90. Furukawa TA, Watanabe N, Omori IM. What (no) differences in responses to three classes of psychotropics can teach us about distinctions between generalized anxiety disorder and major depressive disorder. In: Goldberg DP, Kendler KS, Sirovatka P, Regier DA, eds. *Diagnostic Issues in Depression and Generalized Anxiety Disorder: Refining the Research Agenda for DSM-V.* Washington, DC: American Psychiatric Association; 2010.

91. Morilak DA, Frazer A. Antidepressants and brain monoaminergic systems: a dimensional approach to understanding their behavioural effects in depression and anxiety disorders. *Int J Neuropsychopharmacol*. 2004;7(2):193-218.

92. Balázs J, Miklósi M, Keresztény A, et al. Adolescent subthreshold-depression and anxiety: psychopathology, functional impairment and increased suicide risk. *J Child Psychol Psychiatry*. 2013;54(6):670-677.

93. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. *Arch Gen Psychiatry*. 2005;62(1):66-72.

94. Pickles A, Rowe R, Simonoff E, Foley D, Rutter M, Silberg J. Child psychiatric symptoms and psychosocial impairment. *Br J Psychiatry*. 2001;179:230-235.

95. Plomin R, Haworth CM, Davis OS. Common disorders are quantitative traits. *Nat Rev Genet*. 2009;10(12):872-878.

96. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and generalized anxiety disorder. *Arch Gen Psychiatry*. 1992;49(9):716-722.

97. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A population-based twin study of major depression in women: the impact of varying definitions of illness. *Arch Gen Psychiatry*. 1992;49(4):257-266.

98. Merrell KW, McClun LA, Kempf KKG, Lund J. Using self-report assessment to identify children with internalizing problems: validity of the internalizing symptoms scale for children. *J Psychoed Assess*. 2002;20:223-239.

99. Michael KD, Merrell KW. Reliability of children's self-reported internalizing symptoms over short to medium-length time intervals. *J Am Acad Child Adolesc Psychiatry*. 1998;37(2):194-201.

100. Plomin R, DeFries JC, McClearn GE, McGuffin P. *Behavioral genetics*. New York, NY: Worth Publishers; 2008.