

Original Investigation

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

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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.

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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-occur²⁻⁴ and are rarely diagnosed in isolation.^{2,5,6} They share multiple risk factors⁷ including substantial genetic overlap.⁸⁻¹² These observations argue against diagnosis-specific etiology of depression and anxiety. However, anxiety is heterogeneous¹ 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 com-

bine 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 twin 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 OpenMx⁷⁰ 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) ($AIC = \chi^2 - 2df$; $BIC = \chi^2 - k \ln[n]$), 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

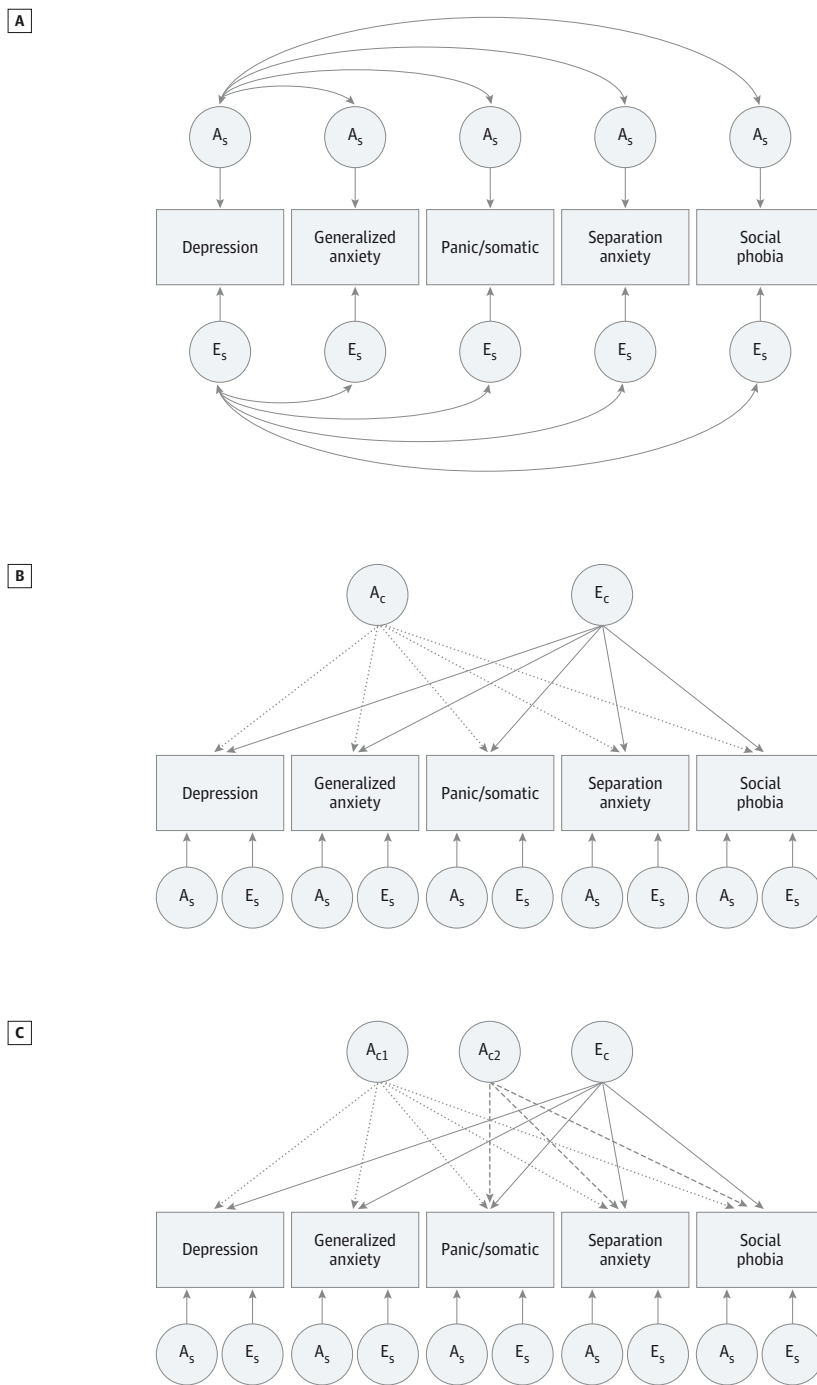
Full correlations at all ages showed that depression symptoms were significantly associated with all anxiety subscales (Table 2). In childhood and adolescence, depression symptoms showed significantly stronger correlations with generalized anxiety symptoms ($r = 0.36$ to 0.60) than with all other subscales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

Correlation	Childhood ^{b,c}		Adolescence ^{b,c}		Young Adulthood ^{b,c}
			Mean Age, y		
	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 unidimensional¹⁹⁻²² and bidimensional²⁶⁻³⁰ 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	25 576.53
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 non-shared 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}

Subscale	Common Factors			Specific Influences		
	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}

Subscale	Common Factors			Specific Influences	
	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 exclud-

ing 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 psychopathology⁹²⁻⁹⁴ 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.

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