The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence and young adulthood

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Abstract

Importance: The recently published DSM-5 continues to classify 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). Little is known, however, about the phenotypic and genetic structure of internalizing psychopathology in children and adolescents.

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

Design: Two population-based prospective longitudinal twin/sibling studies.

Setting: United Kingdom

Participants: Child sample: 578 twins, mean ages approximately 8 and 10 years at waves 1 and 2 respectively. Adolescent and early adulthood sample at 3 waves: 2619 twins, mean ages 15, 17 and 20 years at each wave respectively.

Main Outcome 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; this association broadened to panic and social phobia symptoms in adolescence; and all anxiety subscales in young

adulthood. 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. Findings affirm the need to continue examining the classification of mood and anxiety disorders in diagnostic systems.

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Introduction

The recent publication of DSM-5[1] has been central to the debate regarding the classification of depression and anxiety disorders. 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 given age changes in internalizing disorders[5,7,13], it remains unclear whether all anxiety types are equally associated with depression across development[14-18]. In an effort to improve diagnostic classification, the current study investigates the etiological structure of internalizing disorder symptoms in childhood, adolescence and early adulthood.

The majority of 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 two factors may be underpinned by separate genetic influences[31]. Importantly, 'fear' and 'distress' are generally highly correlated with each other, thus the two conceptualizations are not mutually exclusive.

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] _ENREF_25, others identify the distress and

fear dimensions[35, 36], and one study found that depression and anxiety disorders generally cluster into DSM-related categories[37]. Twin and family studies largely provide evidence for shared etiology of mood and anxiety disorder symptoms in young people, in line with the unidimensional conceptualization[38-43] _ENREF_33 _ENREF_35. 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 of 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 and post adolescence[51-57], with one 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 examine these important taxonomic issues by employing a genetically informed design to investigate the structure of internalizing psychopathology, cross-sectionally at multiple ages: childhood, adolescence and early adulthood. This is the first study to combine five waves of phenotypic and genetic data on depression symptoms and five 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 three alternative models, based on previous research: DSM-5-related structure, unidimensional and bidimensional (fear and distress) models. Given mixed findings and broad age ranges of previous research, the current study tested alternative models in an exploratory manner.

Methods

Participants

The analyses use data from two longitudinal twin studies: waves 1 and 2 from the Emotions, Cognitions, Heredity and Outcome study (ECHO, child twin sample) and waves 2-4 from the Genesis 1219 study (G1219: adolescent/young adult twin and sibling sample). Full recruitment details are provided elsewhere[58, 59] (see eMethods). Both studies were given ethical approval by the appropriate committees[1]. Informed consent was obtained from parents of children under 16 years and from adolescents over 16. Sample characteristics are presented in Table 1.

Measures

Depression

Child participants completed the Children's Depression Inventory[60]; 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[61]; a 13-item self-report measure assessing how often depressive symptoms occurred in the past two weeks. Responses were summed to give total depression scores. Both measures demonstrate good reliability and validity[60, 61] ENREF_27.

[1] The Research Ethics Committee of the Institute of Psychiatry, Kings College, London, South London and Maudsley NHS Trust and of Goldsmiths University, London.

Anxiety

Children's anxiety disorder symptoms were measured using the Screen for Child Anxiety Related Emotional Disorders[62]. 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[63]; a 38-item self-report questionnaire tapping common anxiety symptoms. Adults completed the Revised Symptoms of Anxiety Scale[64], an age-appropriate version of the Revised Child Anxiety and Depression Scale[65], consisting of 36 self-report items designed to assess DSM-4 anxiety and depressive disorder symptoms. Responses were summed to create four DSM-4-related anxiety subscale scores: generalized anxiety, panic/somatic symptoms, separation anxiety and social anxiety. All measures have sound psychometric properties[62-65] _ENREF_29 _ENREF_30.

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

Analyses

Phenotypic analyses

Descriptive statistics were conducted using Stata[66]. 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 due to high co-variance.

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 allows estimations of the influences of additive genetics (A), shared environment (C) and non-shared environment (E). Quantitative genetic methods are described comprehensively elsewhere[67].

Models were fitted using OpenMx[68] within R (www.R-project.org[69]), a structural equation modeling package for the analysis of genetically informative data. Sampling weights were incorporated into child analyses, although did not influence the results in a manner that would alter interpretation[70]. The weight controls for biases due to selection criteria. Lower weights were assigned to individuals from categories over-represented in the sample, and higher weights to individuals from categories under-represented, relative to the population distribution. As is standard in model fitting analysis, variables were regressed for age and sex[71], and any with skew greater than 1 were transformed.

Univariate genetic analyses were conducted on all variables at each wave. Due to sample size, sex differences were only examined in G1912. Scalar sex differences were tested which examine whether males and females showed differences in variance. A scalar model was fitted in twin modelling 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 sub-scales 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 1a), 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 A, C and E influences on each of the scales and tests whether the correlation between them is due to correlations amongst 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 amongst the variables can be mediated via genetic or environmental routes.

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

The third model was a two-factor independent pathway model (Figure 1c). This model is similar to the one-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 two common genetic factors ('distress' and 'fear') and one common non-shared 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 (-2LL) of the observations. This is not an overall measure of fit, but provides a relative measure of fit, since differences in -2LL between models are distributed as χ^2. Therefore, to examine the overall fit of the genetic model we compared the -2LL to 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 sub-models was assessed by $\chi 2$ difference tests, the Akaike's and the Bayesian's Information Criterion (AIC= $\chi 2$ – 2df, BIC= $\chi 2$ – kln(n)) with lower $\chi 2$ values, and more negative AIC and BIC values suggesting a better fit. If the difference between the AIC of two models was less than 10, the more parsimonious

model was selected[72]. Independent pathway models are nested in the correlated factors solution, and the one-factor independent pathway model is nested in the two factors 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), and including an additional anxiety subscale: fear of physical injury (only available at the two adolescent time-points, eTable 2).

Results

Results focus on the association between depression and the different anxiety subscales. The phenotypic and genetic associations amongst the anxiety subscales are presented elsewhere[70, 73].

Phenotypic results

Full correlations at all ages showed that depression symptoms were significantly associated with all anxiety subscales (Table 2a). In childhood and adolescence, depression symptoms showed significantly stronger correlations with generalized anxiety symptoms (r=.36 to .60) than with all other subscales, except panic symptoms (r= .28 to .57).

Partial correlations that controlled for all other variables within times are shown in Table 2b. In childhood, when controlling for concurrent associations, depression symptoms were only significantly associated with generalized anxiety symptoms (r=.21 and .20). At 15 years, partial correlations revealed that depression symptoms were significantly associated with three anxiety subscales: generalized anxiety (r=.19), panic (r=.24) and social phobia (r=.14) symptoms. At mean age 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-significant and non-shared environmental influences were large (eTable 3). Multivariate model fitting results are presented in Table 3. Shared environmental influences were non-significant 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 AE models.

In childhood, the most restrictive one-factor independent pathway model was the best fitting model (Table 4a). 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 non-shared environmental influences on each symptom.

In adolescence, the least restrictive model, the correlated factors solution, showed the best fit to the data, in line with DSM-5 conceptualization (Table 4b). Genetic correlations were mostly large. Depression symptoms generally had higher genetic correlations with generalized anxiety (r=.71 and .74), panic (r=.78 and .61) and social phobia (r=.66 and .53) than with separation anxiety (r=.52 and .15) symptoms. Non-shared environmental correlations were generally moderate. Genetic influences explained a substantial proportion of the phenotypic correlation between depression and anxiety subscales (36-100%).

In young adulthood, a two-factors independent pathway model showed the best fit to the data, in line with a bidimensional conceptualization (Table 4c). 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 non-shared

environmental factor loaded significantly on all variables, but there were also significant unique non-shared environmental influences on each variable.

Discussion

The current study is the first to investigate the phenotypic and genetic structure of internalizing disorders symptoms at three 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 etiological structures of internalizing disorder symptoms at three 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, depression was associated with three anxiety disorder subscales: generalized anxiety disorder, panic and social phobia symptoms. At this developmental stage, the etiological 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] ENREF_25. 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 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] ENREF_44 ENREF_37.

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 two 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 debate as to whether generalized anxiety disorder ought to be classified together with depression[14-17], and 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 generalized anxiety disorder symptoms was the only subscale 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[74], 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[75-77]. The results provide preliminary support for 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[78]. Conversely, the difference in the genetic results pre and post adolescence also provides a preliminary argument for narrowing the phenotypic definitions by age[79].

A key clinical implication of our findings is the support for transdiagnostic treatment approaches for anxiety and depression disorders, which are designed to target common elements of several disorders in one protocol[80-85]. The developmental pattern of the data suggest 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 etiological factor is in agreement with the findings that internalizing disorders respond to similar interventions and therapies[23, 84-89] _ENREF_85.

The genetically-informative, representative samples and multiple time points are 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, given internal replication of results across the two time points, interpretations seem broadly applicable for childhood. Second, the inclusion of siblings in G1219 meant that 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[90-92] and given that common mental disorders are quantitative traits[93], there is evidence that differently defined internalizing problems have the same etiology[8, 94, 95]. Fourth, our study included self-report measures, allowing comparisons across waves. Whilst studies have shown that young children can accurately report on their own internalising symptoms[96, 97], including parent report measures at these waves may have strengthened our findings. Last, there are limitations inherent to the twin design, discussed comprehensively elsewhere[98]. These have minimal and contrasting effects on parameter estimates which should therefore be taken as indicative rather than absolute.

To conclude, 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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Monika A 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

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Figures Legends

Figure 1 – Diagrams presenting the three multivariate models fitted to the data: (a) correlated factors solution (DSM-5 conceptualisation), (b) one-factor independent pathway model (unidimensional conceptualisation), (c) two-factor independent pathway model (bidimensional 'distress' and 'fear' conceptualisation).

Note:

A_c *and* 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 – non-shared environmental influences acting via a common factor on all variables, E_s – non-shared environmental influences acting on a specific variable.

Figure for illustrative purposes only. Only the genetic and non-shared environmental associations on a selection of variables are shown.

Table 1. Sample characteristics and descriptive statistics.

Sample	ECHO			G1219	
Wave	**Wave 1** Child	**Wave 2** Child	**Wave 2** Adolescent	**Wave 3** Adolescent	**Wave 4** Young adult
N (pairs)[a]	300	250	1,372	866	896
Female / Male pairs (%)	169.5 (57) / 130.5 (43)	141 (56) / 109 (44)	768 (56) / 604 (44)	520 (60) /346 (40)	547 (61) / 349 (39)
Age: Mean (years, months) (range)	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[b] (MZ/DZS/DZO/Sib)	100/82/117/0	83/69/98/0	350/313/334/330[2]	234/207/232/182	230/214/232/201

	N	**Mean (SD)**	**Skew**	**Kurtosis**	**α**	**N**	**Mean (SD)**	**skew**	**kurtosis**	**α**	**N**	**Mean (SD)**	**Skew**	**Kurtosis**	**α**	**N**	**Mean (SD)**	**skew**	**kurtosis**	**α**	**N**	**Mean (SD)**	**skew**	**kurtosis**	**α**
Depression	575	10.27 (6.94)	.91	3.66	.81	499	8.22 (5.82)	1.06	4.07	.82	2630	8.08 (6.65)	1.35	4.86	.86	1590	6.25 (5.33)	1.14	3.90	.79	1549	6.45 (5.73)	1.26	4.22	.90
Generalized Anxiety	578	5.52 (3.51)	.42	2.71	.69	489	5.08 (3.46)	.67	3.12	.76	2632	5.17 (2.98)	.87	4.12	.77	1555	4.87 (2.92)	.81	3.82	.78	1552	4.81 (2.97)	.82	3.73	.70
Panic	578	7.15 (4.53)	.57	2.82	.75	489	5.71 (3.93)	.86	3.89	.76	2619	2.82 (3.26)	1.83	7.48	.77	1565	1.40 (2.24)	2.55	11.53	.78	1552	3.57 (3.61)	2.13	9.83	.86
Separation Anxiety	578	7.46 (3.53)	.11	2.40	.69	489	6.06 (2.24)	.42	2.84	.69	2622	2.90 (2.50)	1.35	5.68	.67	1568	2.72 (1.42)	1.02	4.76	.66	1551	2.65 (2.91)	1.83	7.73	.77
Social Anxiety	578	6.80 (2.96)	-.12	2.68	.51	489	6.27 (3.03)	.05	2.74	.58	2625	5.97 (3.31)	.52	2.95	.72	1572	4.37 (2.70)	.54	2.85	.78	1551	10.91 (5.45)	.43	2.89	.83

Note:

MZ - monozygotic; *DZS* - dizygotic (same-sex pairs); *DZO* - dizygotic (opposite-sex pairs); *Sib* – siblings

Table 1 (continued). Sample characteristics and descriptive statistics.

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

[b] Twin pair zygosity was identified in both samples using a combination of parent-rated questionnaires 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; wave 4 = 19). These pairs were excluded from genetic analyses.

Different measures were used at different time points, thus the means cannot be compared across certain time points. In order to check for measurement effects, longitudinal correlations between anxiety subscales scores are presented in eTable 4. The results suggest comparable continuity of anxiety symptoms scores within and across anxiety measures

Results presented on untransformed variables for comparison with other published samples.

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

Twin pair zygosity was identified in both samples using a combination of parent-rated child[99] and adolescent[100] questionnaires, and DNA sequencing in uncertain cases.

Table 2 – Full and partial correlations between depression and anxiety subscales in childhood, adolescence and early adulthood.

	Childhood (8 years)	Childhood (10 years)	Adolescence (15 years)	Adolescence (17 years)	Young Adulthood (20 years)
(a) Full Correlations with Depression					
Generalized Anxiety	**.40 (.33-.47)**	**.36 (.31-.46)**	**.60 (.58-.62)**	**.59 (.56-.62)**	**.56 (.53-.59)**
Somatic/Panic	**.32 (.25-.39)**	**.28 (.20-.36)**	**.57 (.54-.60)**	**.48 (.44-.52)**	**.51 (.47-.55)**
Separation Anxiety	**.24 (.16-.32)**	**.23 (.15-.31)**	**.42 (.39-.45)**	**.16 (.11-.21)**	**.50 (.46-.54)**
Social Phobia	**.18 (.10-.26)**	**.18 (.09-.26)**	**.47 (.44-.50)**	**.44 (.40-.48)**	**.54 (.50-.57)**
(b) Partial Correlations with Depression					
Generalized Anxiety	**.21 (.13-.29)**	**.20 (.11-.28)**	**.19 (.15-.23)**	**.29 (.24-.34)**	**.14 (.09-.19)**
Somatic/Panic	.07 (-.01-.15)	.04 (-.05-.13)	**.24 (.20-.28)**	**.17 (.12-.22)**	**.15 (.10-.20)**
Separation Anxiety	-.03 (-.11-.05)	.04 (-.05-.13)	-.02 (-.06-.02)	**-.14 (-.19--.09)**	**.06 (.01-.11)**
Social Phobia	-.05 (-.13-.03)	-.02 (-.11-.07)	**.14 (.10-.18)**	**.16 (.11-.21)**	**.19 (.14-.24)**

Table 2 (continued) – Full and partial correlations between depression and anxiety subscales in childhood, adolescence and early adulthood.

Note:

The childhood sample comes from the ECHO study, the adolescent sample comes from waves 2-3 and the young adult sample comes from wave 4 from the G1219 study. Mean ages provided in the headings.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations (in bold). Non-overlapping CIs mean significant difference between the values. The difference in CIs width between the ECHO and G1219 time points reflects larger sample size of G1219 which results in greater power to estimate the parameters precisely.

Partial correlations controlled for all other anxiety variables within time.

Results presented on untransformed variables for comparison with other published samples. The correlations between anxiety disorder subscales are discussed elsewhere[70, 73].

The additional analyses inclusive of fear of physical injury symptoms (at mean ages 15 and 17) are presented in eTable 2.

Table 3 – Multivariate model fit statistics in childhood, adolescence and early adulthood.

			Comparison to Saturated Model			Comparison to Correlated Factors Solution			Comparison to 2 Factors Independent Pathway Model				
	-2LL	df	χ^2	Δ df	p-value	χ^2	Δ df	p-value	χ^2	Δ df	p-value	AIC	BIC (size-adjusted)
Childhood (8 years)													
Saturated Model	12970.90	2747										7476.91	13299.68
Correlated Factors Solution	13084.65	2827	113.75	80	.01							7430.65	13211.10
2 Factors Independent Pathway Model	13092.67	2839	121.77	92	.02	8.02	12	0.78				7414.67	13188.77
1 Factor Independent Pathway Model	**13094.21**	**2842**	**123.31**	**95**	**.03**	**9.56**	**15**	**0.85**	**1.54**	**3**	**0.67**	**7410.21**	**13182.73**
Childhood (10 years)													
Saturated Model	6919.34	2091										2737.34	7217.04
Correlated Factors Solution	7047.12	2171	127.78	80	<.01							2705.12	7161.62
2 Factors Independent Pathway Model	7060.67	2183	141.33	92	<.01	13.55	12	0.33				2694.67	7147.69
1 Factor Independent Pathway Model	**7068.86**	**2186**	**149.52**	**95**	**<.01**	**21.74**	**15**	**0.11**	**8.19**	**3**	**0.04**	**2696.86**	**7144.15**
Adolescence (15 years)													
Saturated Model	34539.26	12183										10173.26	37116.75
Correlated Factors Solution	**35207.38**	**12664**	**668.12**	**481**	**<.01**							**9879.38**	**35400.69**
2 Factors Independent Pathway Model	35245.11	12671	705.85	488	<.01	37.73	7	<.01				9903.11	35403.73
1 Factor Independent Pathway Model	35297.10	12674	757.83	491	<.01	89.72	10	<.01	51.99	3	<.01	9949.10	35440.84
Adolescence (17 years)													
Saturated Model	19082.97	7202										4678.97	21660.45
Correlated Factors Solution	**19758.02**	**7683**	**675.05**	**481**	**<.01**							**4392.02**	**19951.33**
2 Factors Independent Pathway Model	19823.33	7690	740.36	488	<.01	65.31	7	<.01				4443.33	19981.94
1 Factor Independent Pathway Model	19844.34	7693	761.37	491	<.01	86.32	10	<.01	21.01	3	<.01	4458.34	19988.08
Young Adulthood (20 years)													
Saturated Model	22999.04	7065										8869.04	25576.53
Correlated Factors Solution	23556.80	7546	557.76	481	<.01							8464.80	23750.11
2 Factors Independent Pathway Model	**23566.13**	**7553**	**567.09**	**488**	**.01**	**9.33**	**7**	**0.23**				**8460.13**	**23724.74**
1 Factor Independent Pathway Model	23587.09	7556	588.05	491	.01	30.29	10	<.01	20.96	3	<.01	8475.09	23730.83

Table 3 (continued) – Multivariate model fit statistics in childhood, adolescence and early adulthood.

Note:

The childhood sample comes from the ECHO study, the adolescence sample comes from waves 2-3 and the young adult sample comes from wave 4 from the G1219 study. Mean ages provided in the headings.

-2LL – minus twice the log likelihood; *df*- degrees of freedom; $\Delta\ df$ – degrees of freedom difference; *p* – probability; *AIC* – Akaike's information criterion; *BIC* – Bayesian's information criterion.

The best fitting model (shown in bold) was selected based on the principle of parsimony and lowest AIC and BIC value. A difference in AIC between two 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 to the higher AIC model [72]. At age 10 the difference between AIC for 1 and 2 factors independent pathway models was 2.19, thus the 1 factor independent pathway model was selected, as it is more parsimonious.

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.

AE models are presented for the adolescent and young adult samples, as C influences were not significant (eTable 3), and were dropped from the multivariate ACE models without a significant deterioration of the fit (eTable 5).

Table 3 (continued) – Multivariate model fit statistics in childhood, adolescence and early adulthood.

The analyses were repeated excluding siblings to narrow the age-ranges (at mean ages 15, 17 and 20 years, see eTable 1), and including an additional anxiety subscale: fear of physical injury (at mean ages 15 and 17 years, see eTable 2). The pattern of effects and the best fitting models remained the same at each time point.

Table 4 – Model fitting results: (a) One factor independent pathway model results in the child sample (8 / 10 years old), (b) Correlated factor solution results in adolescents (15 / 17 years old), (c) Two factors independent pathway model results in young adults (20 years old).

(a) ONE FACTOR INDEPENDENT PATHWAY MODEL RESULTS IN THE CHILD SAMPLE (8 / 10 YEARS OLD)

	Common Factors			Specific Influences		
	A_c	C_c	E_c	A_s	C_s	E_s
Depression	.00 (.00-.19) / .02 (.00-.42)	.15 (.04-.33) / .15 (.00-.52)	.18 (.09-.30) / .04 (.00-.12)	.17 (.00-.35) / .00 (.00-.30)	.00 (.00-.22) / .21 (.00-.37)	.49 (.37-.65) / .58 (.45-.69)
Generalized Anxiety	.13 (.01-.30) / .06 (.00-.44)	.03 (.00-.15) / .14 (.00-.29)	.35 (.22-.49) / .35 (.20-.77)	.01 (.00-.12) / .01 (.00-.16)	.00 (.00-.07) / .00 (.00-.08)	.47 (.36-.56) / .43 (.12-.54)
Panic/Somatic	.16 (.00-.40) / .03 (.00-.45)	.07 (.00-.23) / .11 (.00-.31)	.47 (.31-.63) / .50 (.19-.72)	.04 (.00-.14) / .08 (.00-.24)	.00 (.00-.08) / .00 (.00-.17)	.25 (.15-.35) / .27 (.11-.54)
Separation Anxiety	.27 (.10-.42) / .08 (.00-.55)	.00 (.00-.10) / .08 (.00-.28)	.26 (.15-.40) / .22 (.03-.34)	.00 (.00-.11) / .14 (.00-.27)	.00 (.00-.05) / .00 (.00-.14)	.46 (.36-.55) / .48 (.36-.63)
Social Phobia	.12 (.00-.24) / .38 (.00-.53)	.00 (.00-.08) / .01 (.00-.27)	.28 (.17-.46) / .21 (.09-.40)	.00 (.00-.07) / .00 (.00-.42)	.00 (.00-.04) / .00 (.00-.25)	.59 (.49-.68) / .40 (.27-.54)

(b) CORRELATED FACTOR SOLUTION RESULTS IN ADOLESCENTS (15 / 17 YEARS OLD)

		Generalized Anxiety	Panic	Separation Anxiety	Social Phobia
Depression	Genetic Correlations	.71 (.63-.78) / .74 (.63-.85)	.78 (.70-.86) / .61 (.48-.73)	.52 (.43-.61) / .15 (-.01-.32)	.66 (.57-.75) / .53 (.38-.66)
	Environmental Correlations	.40 (.33-.47) / .41 (.32-.50)	.34 (.27-.41) / .36 (.26-.45)	.34 (.27-.42) / .00 (-.11-.11)	.30 (.22-.38) / .36 (.27-.45)
	Proportion of r_{ph} due to A	.62 (.53-.71) / .58 (.45-.69)	.66 (.57-.74) / .57 (.41-.71)	.58 (.47-.69) / 1.00[a]	.66 (.56-.76) / .50 (.34-.64)
	Proportion of r_{ph} due to E	.38 (.29-.47) / .42 (.31-.55)	.34 (.26-.43) / .43 (.29-.58)	.42 (.31-.53) / .00[a]	.34 (.24-.44) / .50 (.36-.66)

(c) TWO FACTORS INDEPENDENT PATHWAY MODEL RESULTS IN YOUNG ADULTS (20 YEARS OLD)

	Common Factors			Specific Influences	
	A_{c1}	A_{c2}	E_c	A_s	E_s
Depression	.26 (.17-.35)		.19 (.12-.27)	.15 (.08-.22)	.41 (.34-.48)
Generalized Anxiety	.33 (.24-.43)		.34 (.25-.44)	.07 (.02-.12)	.26 (.20-.32)
Panic	.26 (.17-.35)	.02 (.01-.08)	.29 (.20-.39)	.05 (.00-.12)	.37 (.31-.44)
Separation Anxiety	.27 (.18-.37)	.04 (.01-.14)	.27 (.19-.37)	.05 (.00-.13)	.36 (.29-.43)
Social Phobia	.40 (.30-.49)	.07 (.01-.12)	.26 (.18-.34)	.00 (.00-.00)	.27 (.22-.33)

Table 4 (continued) – Model fitting results: (a) One factor independent pathway model results in the child sample (8 / 10 years old), (b) Correlated factor solution results in adolescents (15 / 17 years old), (c) Two factors independent pathway model results in young adults.

Note:

[a] CIs not available due to zero environmental correlation between depression and separation anxiety symptoms at 17 years old.

A_c *and* 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, 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 – non-shared environmental influences acting via a common factor on all variables, E_s – non-shared environmental influences acting on a specific variable, r_{ph} – phenotypic correlation.

95% Confidence Intervals (CIs) are presented in brackets. CIs not inclusive of zeros indicate significant correlations. Non-overlapping CIs mean significant difference between the values. The difference in CIs width between the ECHO and G1219 time points reflects larger sample size of G1219 which results in greater power to estimate the parameters precisely.

In the child sample, C was modeled and submodel comparisons revealed that C 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 C parameter in child sample in order to avoid artificially inflating A estimates.

Table 4 (continued) – Model fitting results: (a) One factor independent pathway model results in the child sample (8 / 10 years old), (b) Correlated factor solution results in adolescents (15 / 17 years old), (c) Two factors independent pathway model results in young adults.

AE models are presented for the adolescent and young adult samples, as C influences were not significant (eTable 3), and were dropped from the multivariate models without a significant deterioration of the fit (eTable 5). The AIC values suggest that dropping C lead to improvement of the model fit at these three waves.

Depression at time 2 in child sample (ECHO) showed 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 A and C in the ECHO sample.

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