Heritability of Anxious-Depressive and Withdrawn Behavior: Age-Related Changes During Adolescence

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Objective: To explain the differential course of anxiety and depression in individuals from childhood to adulthood by examining age-related changes in the genetic and environmental etiology of anxious and depressive symptoms. **Method:** A sample of 1470, 1839, and 2023 Dutch twins aged 12, 14, and 16 years reported on symptoms of anxious depression (AD) and withdrawn behavior (WB), using the Youth Self Report (YSR). AD and WB were analyzed with bivariate cross-sectional genetic models for each age group to obtain estimates of the relative influence of genes (A), shared (C), and nonshared (E) environment. **Results:** The best-fitting models revealed no difference between heritability estimates in boys and girls. Familial clustering at age 12 years was explained by genetic and shared environmental factors. At ages 14 and 16 years, genetic factors were sufficient to explain familial clustering, shared environmental effects were absent. Genetic influences on AD and WB correlated highly. **Conclusions:** These findings are in agreement with earlier studies on age-specific effects of genes and shared environment on anxiety, depression, and withdrawn behavior in childhood and adolescence. The current study demonstrated that the decrease in the role of shared environment occurs after age 12. Hormonal changes accompanying the onset of puberty do not seem to explain the change in risk factors, as in 90% of the subjects puberty had already started. More knowledge on age-specific risk factors may offer opportunities for therapeutic interventions. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(3):248–255. **Key Words:** Anxious depression, Withdrawn behavior, Adolescence, Twins, Genetics.

Anxiety disorders and depression are common disorders throughout the lifespan. Prevalence studies have established that between ages 5 and 17, approximately 8% of children experience any anxiety disorder. Nearly 5% of individuals in this age range experience major depression, but the prevalence tends to increase with age (peaking in adolescence).[1] In adult population-based studies, lifetime prevalence estimates for any anxiety disorder (including panic disorder, phobias, obsessive compulsive disorder, and generalized anxiety disorder) and major depression are approximately 19% and 16%, respectively.[2,3]

Longitudinal studies have established that anxiety disorders during childhood are moderately stable and are predictive of other mental health problems, especially depression, in later life (reviewed by Rapee et al.[4]). However, these studies have also shown that childhood anxiety disorders may disappear over time without further sequelae, and that anxiety disorders may present themselves in later life, i.e., after adolescence.[4] Similar results hold for major depression, although the effects of childhood or adolescent depression seems to be more deleterious.[5,6] Comorbidity within anxiety disorders and comorbidity of anxiety disorders with depression is frequent in both children and adults.[7-11] Research suggests that this may be due to common, mostly genetic, risk factors.[12]

Changes in the influence of genetic and environmental risk factors with age explain in part the differential course of anxiety and depression in individuals from childhood to adulthood. Specifically, reviews have established that genetic factors contribute to individual differences in anxiety and depression in both childhood and

adulthood. However, the contribution of shared environmental factors is limited to childhood.[4,13-18]

Studies performed of anxiety and depression in children and adolescents, however, have not yielded consistent results. Most studies in which the samples were divided into two or more age groups have tended to find that familial resemblance is due to genetic and shared environmental factors in childhood, whereas in adolescence genetic factors are important but shared environmental factors are not.[19-24] Associated with the decrease in shared environmental effects is a general increase in heritability of anxiety and depression. This finding is supported by a meta-analysis [25]. However, the results are inconsistent in that studies have also reported a decreased role of genetic and an increased role of shared environmental factors in the development from childhood to adolescence.[26] In addition, some studies have reported distinct changes in boys and girls,[29,30] whereas other studies reported no clear changes at all.[27,28]

This inconsistency may be caused by the use of different instruments to measure the phenotypes of interest. In addition, the measures differ with respect to informant or rater (i.e., the parent, teacher, or the child her- or himself). Reviews of studies of anxiety and depression have suggested that estimates of heritability based on parental ratings are higher than the heritabilities based on child self-report.[4,13,15] In addition, estimates of shared environmental influences tend to be lower when based on parental ratings.

Another source of inconsistency may be variation in the age range of the participants. Almost all studies divided the children into two age cohorts: below and above 11 or 12 years of age. Four studies were exceptions, of which three found results that differed from those of most other studies.[20,26-28] Studies performed in children at ages of 3, 7, 10, and 12 indicated that the effect of the common environment is still present at age 12 for different measures of anxiety and depression.[31-33] Thus the standard cut-off age of 11 or 12 may produce an age group that is actually heterogeneous in the sense that common environmental effects may be present in the 12 year olds but not (or to a lesser degree) in children over 12. Thus, it is important to retain an appropriate age resolution in the study of age changes in the effects of genetic and environmental influences on anxiety and depression.

The present aim is to study the course of genetic and environmental influences on anxiety and depression at 12, 14, and 16 years. In a population-based sample of monozygotic and dizygotic Dutch adolescent twins, anxious depression (AD) and withdrawn behavior (WB) were measured by self-report at these ages. AD and WB are subscales of the Youth Self Report (YSR)[34] and are highly related to DSM-IV diagnoses of anxiety disorders and depression.[35,36] At each age, a bivariate genetic model was used to estimate the common and phenotype specific influences of genetic (A), shared environmental (C), and unique, nonshared, environmental (E) factors on AD and WB. To address the issue of possible influence of raters on the outcomes, we compared results with those of the analyses of the parental reports on AD and WB for this sample at age 12 years.[32,33]

METHOD

Subjects

All twins were registered at birth by their parents with the Netherlands Twin Register (NTR). Parents and teachers completed questionnaires concerning the twins' behavior up to age 12 years. In this study, the participating twins were born between 1987 and 1996 and completed the YSR at age 12, 14 and 16. Starting in 2004, after parental informed consent was ascertained, questionnaires were sent to the adolescent twins at ages 14 and 16 years. In addition to the ongoing data collection at the NTR, subsamples of twins are also invited to participate in other projects. Within these projects, YSR data were obtained of twins at age 12. Of these twins, 340 twins participated in a project on behavior problems, cognition, and hormones,[37] 806 twins participated in a project on attention problems and hyperactivity,[38] and 392 twins participated in a project on attention and executive functioning.[39] The 12-year olds who took part in the project on attention problems and hyperactivity were selected on the basis of either low or high scores on attention problems. Selection of the other 12-year-olds was based only on place of residence (at reasonable travel distance from Amsterdam). (For a more detailed description of the data collection and the determination of zygosity, see Bartels et al and Boomsma et al.[40,41])

Some overlap exists between the groups. Of all twins who reported on the YSR at age 12, 39% returned the list at age 14 and 21% returned the YSR at age 16. There is no overlap in the samples of twins who returned the YSR at age 14 and 16.

Instrument

AD and WB data came from the YSR, a self-report questionnaire. The YSR is one of the instruments in the Achenbach System of Empirically-Based Assessment (ASEBA). Each ASEBA instrument contains 113 behavioral items with a three-point scale response format. The AD subscale comprises 16 items, with possible responses of 0 (not at all), 1 (a little bit or sometimes), and 2 (a lot or most of the time). The range of the score on the AD subscale of the YSR is therefore from 0 to 32. Two examples of items on this subscale are "I feel lonely" and "I cry a lot." The WB subscale comprises seven items and, given the identical response format and scoring, its range is from 0 to 14. Two examples of items of this subscale are "I am rather alone than with others" and "I refuse to talk."

Statistical Analyses

Because the data of both subscales were positively skewed (L shaped), we used a threshold model to analyze individual differences in the liability to AD and WB. Use of the threshold model requires the discretization of the observed distributions, i.e., the creation of scores that are amenable to the analysis (it is computationally impractical to retain the original scales of 0 to 14 and 0 to 32). Therefore, at each age group, AD and WB scores were categorized into three groups with roughly an equal number of subjects. In this manner, we arrived at ordinal phenotypic scores that were coded 0, 1, and 2. In the liability-threshold model, we require two thresholds to model the three categories of AD and two thresholds to model the three categories of WB. We estimated the thresholds separately in boys and girls to take into account sex differences in AD and WB scores.

The basic assumption underlying the threshold model is that a latent continuous liability underlies the observed categorical variables. The liability is assumed to be standard normally distributed (i.e., mean = 0, SD = 1). Individual differences in the liability are modeled to be due to genetic and environmental effects. The adoption of the threshold model is a generally accepted way to analyze L-shaped distribution of data.[42]

In each age group, we analyzed the MZ and DZ twin data simultaneously in a bivariate model (i.e., including AD and WB). We first fitted a saturated model in which we estimated polychoric correlations between twin pairs within and across traits, allowing differences between sexes and zygosity groups. We used the software package Mx[43] to this end.

Estimating correlations for MZ and DZ twin pairs constituted a first step toward evaluating the relative influence of genetic and environmental factors on trait variances and covariances between traits. MZ twin pairs are genetically identical, whereas DZ twin pairs and nontwin siblings share, on average 50%, of their genetic material. If the MZ twin correlation is higher than the DZ correlation for a certain trait (i.e. within-trait correlation) or between two traits (i.e. cross-twin, cross-trait correlation), we infer that genetic factors (A) contribute to the phenotypic variances and covariance of two phenotypic traits. If DZ correlations are higher than half the MZ correlation, we infer that environmental effects (C) shared by members of the same family are present. Finally, we attribute to nonshared environment effects (E) variance that is not due to genetic or shared environmental factors. These are environmental influences that are not shared by family members. The nonshared environmental variance component also includes measurement error variance.

Next, using structural equation modeling in Mx, we fitted genetic bivariate models to the data. A graphical representation of the genetic model is given in Figure 1. The amount of variance in a single trait and covariance between traits due to A, C, and E can be calculated from the factorloadings a, c, and e. Parameter estimates for a, c, and e were allowed to differ with respect to sex. The results of this model allow us to break down the phenotypic correlation between AD and WD into genetic and environmental correlations.

We performed the analyses using the raw-data likelihood estimation in Mx. We fitted various models that were nested in the sense that one model could be derived from the other by the imposition of one or more constraints on the parameters. We evaluated the differences between (nested) models by inspecting the log-likelihood ratio test (LRT) statistic. This is minus twice the difference of the maximum log-likelihoods of two models. Asymptotically this statistic has a χ^2 distribution, with the degrees of freedom (df) equaling the difference (in df) between the two models. If the p value associated with this statistic is greater than our chosen alpha of .05, we concluded that the constraints associated with the more parsimonious model were tenable.

First, sex differences in the relative influence of A, C, and E were tested by constraining the parameter estimates a, c, and e over sex to be equal and testing whether this constraint led to decrease in goodness of fit. The total variance of the liabilities underlying WB and AD were constrained at 1 by specifying that var(E) = 1 − (var(A) + var(C)). Consequently, when testing for sex differences in the genetic architecture, the test has 7 df. Second, the statistical significance of the genetic and environmental parameters was tested by constraining them at 0.

RESULTS

Descriptives

The number of complete and incomplete twin pairs as a function of age and zygosity is given in Table 1. At ages 12, 14, and 16 years, the total sample consisted of 726 boys and 744 girls, 801 boys and 1,038 girls, and 903 boys and 1,120 girls,

FIGURE 1 Path diagram of the bivariate genetic model. The observed variables are represented with a square (AD = anxious depressive, WB = withdrawn behavior) and the latent factors by circles. The variance within an observed variable is broken down into the three latent factors, and the influence of the latent factors is given by the path coefficients a, c, and e. The total variance of an observed variable is the sum of the squared path coefficients (for AD: $a_{AD}^2 + c_{AD}^2 + e_{AD}^2$). The covariance between the two observed variables is also broken down into a genetic, shared, and nonshared environmental part. The phenotypic correlation is the standardized covariance between the two observed variables; this can be expressed as $rP = a_{AD} \, rA \, a_{WB} + c_{AD} \, rC \, c_{WB} + e_{AD} \, rE \, e_{WB}$. *Note:* A = additive genetic; C = shared environment; E = nonshared environment.
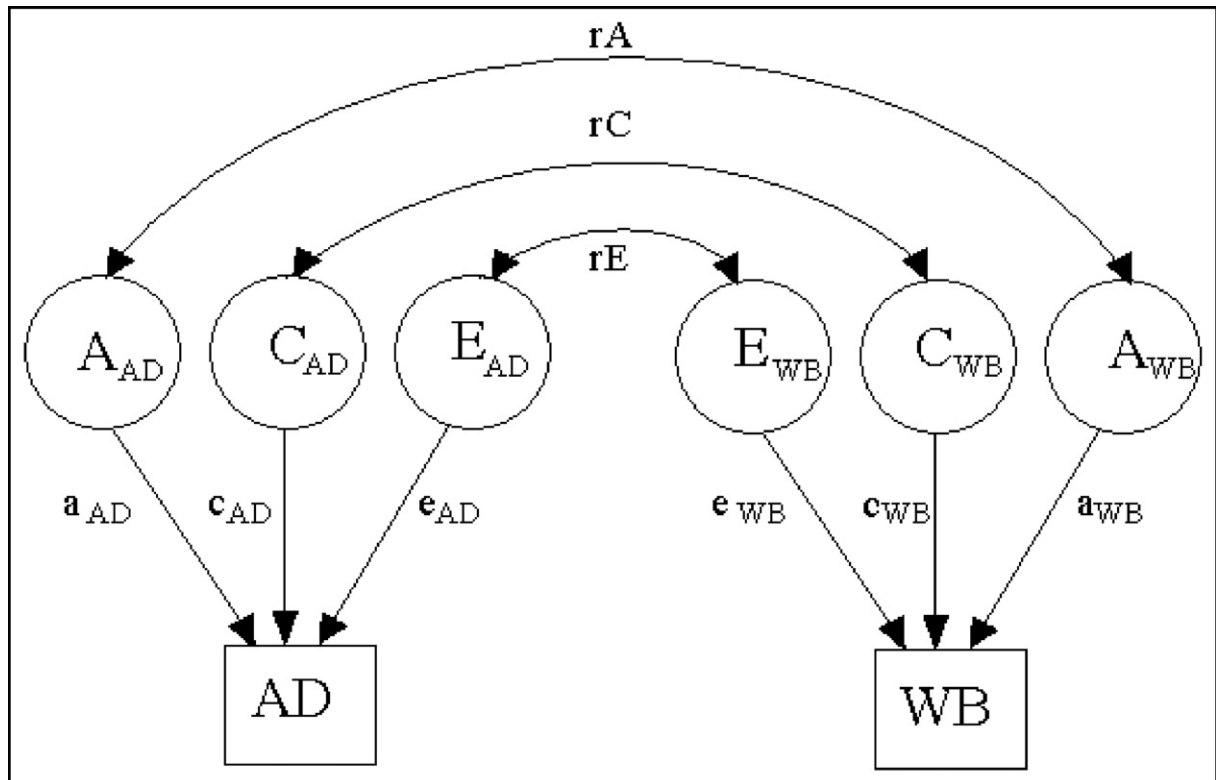
respectively. The mean age in years in each age group was 11.9 (SD = 0.52, range 11 to 13), 14.1 (SD = 0.41), and 16.7 (SD = 0.90, range 16 to 19). Figure 2 shows the mean scores on AD and WB as a function of age and sex. Girls scored higher than boys and, in general, scores tended to increase with age. In view of these results, thresholds were estimated separately per age group

TABLE 1 Twin Correlation for the Categorized Anxious Depression and Withdrawn Behavior Scores for Age 12, 14, and 16, and the Cross-Twin, Cross-Trait Correlations of AD and WB

	Age 12					Age 14					Age 16				
Zygosity	CP (n)	IP (n)	AD	Cross	WB	CP (n)	IP (n)	AD	Cross	WB	CP (n)	IP (n)	AD	Cross	WB
MZM	140	2	0.57	0.41	0.38	130	3	0.53	0.30	0.37	175	13	0.49	0.35	0.44
DZM	138	3	0.39	0.39	0.38	125	7	0.28	0.23	0.23	132	16	0.28	0.25	0.10
MZF	161	3	0.58	0.34	0.46	222	7	0.76	0.51	0.42	215	14	0.57	0.45	0.53
DZF	124	6	0.47	0.45	0.38	143	11	0.42	0.15	0.03	187	14	0.23	0.19	0.18
DOS	162	6	0.17	0.23	0.36	271	29	0.29	0.22	0.17	241	66	0.40	0.28	0.23

Note: AD = anxious depression; CP = complete pairs; DOS = dizygotic twins of opposite sex; DZF = dizygotic female; DZM = dizygotic male; IP = incomplete pairs; MZF = monozygotic female; MZM = monozygotic male; WB = withdrawn behavior.

FIGURE 2 Mean scores on anxious depression and withdrawn behavior as a function of sex and age. AD = anxious depression; WB = withdrawn behavior; YASR = Young Adult Self Report.
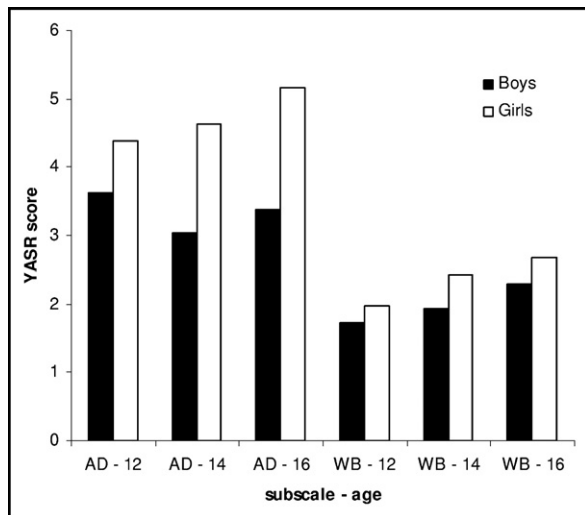
and sex. Phenotypic correlations between AD and WB were high in both sexes at all ages, ranging from 0.59 to 0.69.

Genetic analyses

Twin correlations as a function of age, sex, and zygosity are shown in Table 1. At each age, MZ correlations were higher than DZ correlations, suggesting that genetic factors contribute to indi-

vidual differences in AD and WB. However, the MZ correlations at age 12 were less than twice as high as the DZ correlations, indicating that at that age shared environmental influences may be present. The cross-trait, cross-twin correlations showed largely the same patterns.

Fit statistics of the three full genetic models and the nested submodels can be found in Table 2. There were no significant sex differences in the effect of A, C and E at any age (all *p* values > .05). At age 12, neither effect of A nor C could be dropped from the model ($\chi^2_{(3)}$ = 10.4, p = .02, and $\chi^2_{(3)}$ = 20.6, p < .01, respectively). This means that at age 12 both genetic and shared environmental effect contribute to the phenotypic variance in AD and WB. In AD, 35% of the variance was explained by A, and 21% by C, in WB these estimates were 3% and 38%, respectively. At age 14 and 16, the C component could be dropped from the model ($\chi^2_{(3)}$ = 0, p = 1.00, and $\chi^2_{(3)}$ = 0.8, p = .84). The influence of the genetic factors ranged from 37% to 67% on AD and WB at age 14 and 16. Table 3 contains the estimates of the relative influence of genes, shared, and nonshared environment, with the associated confidence intervals (CI).

The YSR AD and WB scales were highly correlated. This correlation was mostly explained by shared genes. The correlations between genetic factors were 1.0 at age 12, and 0.85 at age 14 and 16. At age 12 the correlation between shared environment influencing AD and WB was also

TABLE 2 Model Fitting Results for Bivariate Genetic Analyses on Anxious Depression and Withdrawn Behavior Scores

	Model	−2LL	Compared with Model	χ^2	Δdf	*p*	AIC
Age 12	0. SAT	5785.7					−74.3
	1. ACE	5794.1	0	8.4	3	.04	−71.9
	2. ACE sex equal	**5804.7**	**1**	**10.7**	**7**	**.15**	**−79.3**
	3. AE	5815.2	2	10.4	3	.02	−74.8
	4. CE	5825.3	2	20.6	3	.00	−64.7
Age 14	0. SAT	7313.6					−46.4
	1. ACE	7317.4	0	4.1	3	.25	−48.6
	2. ACE sex equal	7331.3	1	13.9	7	.05	−52.7
	3. AE	**7331.3**	**2**	**0**	**3**	**1**	**−58.7**
Age 16	0. SAT	7903.4					−210.5
	1. ACE	7911.3	0	7.8	3	.05	−208.7
	2. ACE sex equal	7917.1	1	5.7	7	.57	−220.9
	3. AE	**7917.9**	**2**	**0.8**	**3**	**.84**	**−226.1**

Note: The best model fit is displayed in boldface type. A = additive genetic; AIC = Akaike's Information Criterion; C = common environment; E = unique environment; SAT = Saturated model.

TABLE 3 Standardized Estimates of Amount of Variance Explained by Additive Genetic (A), Common (C), and Unique Environmental (E) Influences and Estimates of Correlations Among These Influences from Bivariate Genetic Analyses

Age	A_{AD}	C_{AD}	E_{AD}	A_{WB}	C_{WB}	E_{WB}	r_A	r_C	r_E
12	0.35 (0.25–0.44)	0.21 (0.09–0.30)	0.45 (0.37–0.56)	0.03 (0.00–0.10)	0.38 (0.25–0.47)	0.60 (0.51–0.68)	1.00 (0.00–1.00)	1.00 (1.00–1.00)	0.50 (0.24–0.59)
14	0.67 (0.46–0.72)	—	0.33 (0.26–0.41)	0.37 (0.18–0.47)	—	0.63 (0.53–0.68)	0.85 (0.75–0.97)	—	0.42 (0.30–0.48)
16	0.55 (0.46–0.63)	—	0.45 (0.37–0.54)	0.45 (0.35–0.54)	—	0.55 (0.46–0.65)	0.85 (0.75–0.94)	—	0.51 (0.40–0.60)

Note: AD = anxious depression; WB = withdrawn behavior.

1.0. Unique environmental factors were less correlated, with estimates around 0.5.

DISCUSSION

The aim of present study was to provide insight into the age-specific genetic and environmental influences on anxiety and depression during adolescence. Our results indicate that, at age 12, familial clustering of AD and WB was due to genetic and shared environmental risk factors, whereas at age 14 and 16, familial clustering was due only to genetic factors. We found no change in the extent to which unique environmental factors played a role from age 12 to age 16, with estimates of explained variance approximating 0.4 for AD and 0.55 for WB. The age-related changes in the effects of A and C are in agreement with most other studies that addressed differences between childhood and adolescence in the genetic and environmental effects on anxiety and depression.[19-24]

Because of the narrow age range of the groups, we could establish that the decrease in the effect of C occurs after age 12. A similar decrease in the influence of C has also been reported with respect to obsessive compulsive symptoms.[44] Several explanations are possible for the change in the relative contributions of risk factors for anxiety and depression in this period in life. One is that the onset of puberty and hormonal changes lead to changes in gene expression influencing the risk for anxiety and depression, i.e., new genes come to expression or other genes come to expression at a higher level. In this case, the change in risk factors of AD and WB would be more or less in synchrony with the start of puberty. We investigated this hypothesis by using self-report data inquiring about pubertal physical changes. Genetic analyses indicated that the decrease in C occurred after age 12. Therefore, one would expect that, if the hormonal changes responsible for the start of puberty play a role in the decrease in the influence of C and the increase in the influence of A, the majority of the 12 year old twins would be prepubescent. However, this was not the case: based on self report, only approximately 10% of the 12-year-old twins appeared to be in Tanner stage 1 (no pubic hair or breast development).[45,46] Thus, in 90% of the present 12-year-olds, puberty had already started. Another explanation is that the influence of C decreases because of a gradual attenuation of the level of parental control and time spent at home and together with the cotwin. This hypothesis requires further investigation.

As the results of similar analyses relating to parental ratings of offspring at 12 on both AD and WB are available, we can compare these results with our present results. Our present estimates of the effects of A and C on AD and WB at age 12 are similar to those obtained using parental reports.[31-33] Only with respect to WB was the present estimate of the effect of C higher than that reported by Hoekstra et al.,[32] who found very little influence of C in the maternal ratings and an influence on the parental ratings amounting to approximately 15% of the variance. These results are consistent with the results of earlier studies that used parental ratings. In these studies, the effect of C were small or absent.[4,13,15]

Discrepancies with results of other studies can be caused by variation in the age range of the participants in the studies. In most other studies, the age ranges are appreciably broader than the present age range.[29,30] However, this does not explain why Kendler et al.[27] and Legrand et al.[28] found no age differences in the estimates of A and C, whereas Gjone et al[26] found an increase in the effect of C with age. Kendler et al.[27] did not actually test the effects of C by age, so they may have missed some effect. They also used parental report in addition to self report. There is no clear explanation for the lack of age specific effects found by Legrand et al.[28] There is also no clear explanation for the effect of C at age 14 to 15 found by Gjone et al[26] in a Norwegian twin sample. However, at least compared with the present Dutch samples, cultural differences may play a role.

We found no sex effects on heritability estimates of AD and WB. The literature is mixed on this point, with most studies reporting higher heritability estimates in girls, although higher heritability estimates in boys and the general absence of sex effects are also reported.[19,23,27,29,30] This discrepancy might be caused by differences in power and heterogeneity in phenotypes.

A limitation of present study is that the overlap in samples was too small to perform longitudinal analyses. In a longitudinal analysis, it is also possible to investigate whether similar or different genetic or environmental factors influence AD and WB over time. Analyses from the longitudinal Swedish Twin Study showed that the genetic factors influencing anxiety and depression differ between childhood and adolescence. The effect of the genetic factors influencing anxiety and depression during childhood is diminished and new genetic factors play a more important role.[20,27,47] In the future, it would be of interest to carry out longitudinal analyses to investigate the genetic and environmental correlation between phenotypes within an age group and over time.

Overall, our study showed that influences of A and C differ over time. This difference in risk factors from childhood to adolescence can partly explain why some individuals experience anxiety and/or depression early in life whereas others do not have such complaints during childhood but begin to experience symptoms during adolescence. Further research is needed to identify the age-specific risk factors, either genetic or environmental, for AD and WB. More knowledge on the age-specific risk factors might facilitate the development of different therapeutic interventions for children of different ages. &

REFERENCES

1. Costello EJ, Egger H, Angold A. 10-year research update review: the epidemiology of child and adolescent psychiatric disorders: I. Methods and public health burden. J Am Acad Child Adolesc Psychiatry. 2005;44:972-986.

2. Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol. 1998;33:587-595.

3. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry. 2005;62:593-602.

4. Rapee R, Schniering C, Hudson J. Anxiety disorders during childhood and adolescence: origins and treatment. Annu Rev Clin Psychol. 2009;5:311-341.

5. Dunn V, Goodyer IM. Longitudinal investigation into childhood- and adolescence-onset depression: psychiatric outcome in early adulthood. Br J Psychiatry. 2006;188:216-222.

6. Pine DS, Cohen P, Gurley D, Brook J, Ma YJ. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch Gen Psychiatry. 1998;55:56-64.

7. Angold A, Costello EJ, Erkanli A. Comorbidity. J Child Psychol Psychiatry. 1999;40:57-87.

8. Brady EU, Kendall PC. Comorbidity of anxiety and depression in children and adolescents. Psychol Bull. 1992;111:244-255.

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

10. Ford T, Goodman R, Meltzer H. The British child and adolescent mental health survey 1999: the prevalence of DSM-IV disorders. J Am Acad Child Adolesc Psychiatry. 2003;42:1203-1211.

11. Kessler RC. Epidemiology of psychiatric comorbidity. In: Tsuang MT, Tohen M, Zahner GE, eds. Textbook in Psychiatric Epidemiology. New York: John Wiley & Sons, Inc.; 1995:179-98.

12. Middeldorp CM, Cath DC, van Dyck R, Boomsma DI. The co-morbidity of anxiety and depression in the perspective of genetic epidemiology. A review of twin and family studies. Psychol Med. 2005;35:611-624.

13. Gregory AM, Eley TC. Genetic influences on anxiety in children: what we've learned and where we're heading. Clin Child Fam Psychol Rev. 2007;10:199-212.

14. Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry. 2001;158:1568-1578.

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

16. Rice F. The genetics of depression in childhood and adolescence. Curr Psychiatry Rep. 2009;11:167-173.

17. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2000;157:1552-1562.

18. Middeldorp CM, Boomsma DI. Genetics and Psychopathology. In: Berntson GG, Cacioppo JT, eds. Handbook of Neuroscience for Behavioral Sciences. New York: Wiley; 2009:1180-1202.

19. Feigon SA, Waldman ID, Levy F, Hay DA. Genetic and environmental influences on separation anxiety disorder symptoms and their moderation by age and sex. Behav Genet. 2001;31:403-411.

20. 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;65:421-429.

21. 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;43:1039-1051.

22. Schmitz S, Fulker DW, Mrazek DA. Problem behavior in early and middle childhood: an initial behavior genetic analysis. J Child Psychol Psychiatry. 1995;36:1443-1458.

23. Scourfield J, Rice F, Thapar A, Harold GT, Martin N, McGuffin P. Depressive symptoms in children and adolescents: changing aetiological influences with development. J Child Psychol Psychiatry. 2003;44:968-976.

24. Thapar A, McGuffin P. A twin study of depressive symptoms in childhood. Br J Psychiatry. 1994;165:259-265.

25. 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; 10:423-433.

26. Gjone H, Stevenson J, Sundet JM, Eilertsen DE. Changes in heritability across increasing levels of behavior problems in young twins. Behav Genet. 1996;26:419-426.

27. Kendler KS, Gardner CO, Lichtenstein P. A developmental twin study of symptoms of anxiety and depression: evidence for genetic innovation and attenuation. Psychol Med. 2008;38:1567-1575.

28. Legrand LN, Mcgue M, Iacono WG. A twin study of state and trait anxiety in childhood and adolescence. J Child Psychol Psychiatry. 1999;40:953-958.

29. Eley TC, Stevenson J. Exploring the covariation between anxiety and depression symptoms: a genetic analysis of the effects of age and sex. J Child Psychol Psychiatry. 1999;40:1273-1282.

30. Silberg J, Pickles A, Rutter M et al. The influence of genetic factors and life stress on depression among adolescent girls. Arch Gen Psychiatry. 1999;56:225-232.

31. Bartels A, van den Oord EJCG, Hudziak JJ, Rietveld AJH, van Beijsterveldt CEM, Boomsma DI. Genetic and environmental mechanisms underlying stability and change in problem behaviors at ages 3, 7, 10, and 12. Dev Psychol. 2004;40:852-867.

32. Hoekstra RA, Bartels M, Hudziak JJ, van Beijsterveldt TCEM, Boomsma DI. Genetic and environmental influences on the stability of withdrawn behavior in children: a longitudinal, multi-informant twin study. Behav Genet. 2008;38:447-461.

33. Boomsma DI, van Beijsterveldt CEM, Hudziak JJ. Genetic and environmental influences on anxious/depression during childhood: a study from the Netherlands Twin Register. Gen Brain Behav. 2005;4:466-481.

34. Achenbach TM, Rescorla LA. *Manual for ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont Research Center for Children, Youth, & Families; 2001.

35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4 ed. Washington DC: APA; 1994.

36. Doyle R, Mick E, Biederman J. Convergence between the Achenbach youth self-report and structured diagnostic interview diagnoses in ADHD and non-ADHD youth. J Nerv Ment Dis. 2007; 195:350-352.

37. Bartels M. *Behavior problems, cognition, and hormones* [dissertation]. Amsterdam: VU University; 2001.

38. Derks EM. *Assessment and genetic aetiology of attention problems, hyperactivity and related disorders* [dissertation]. Amsterdam: VU University; 2006.

39. Polderman TJC, Stins JF, Posthuma D, Gosso MF, Verhulst FC, Boomsma DI. The phenotypic and genotypic relation between working memory speed and capacity. Intelligence. 2006;34:549-560.

40. Bartels M, van Beijsterveldt CEM, Derks EM, *et al.* Young Netherlands Twin Register (Y-NTR): A longitudinal multiple informant study of problem behavior. Twin Res Hum Genet. 2007;10: 3-11.

41. Boomsma DI, De Geus EJC, Vink JM, *et al.* Netherlands Twin Register: from twins to twin families. Twin Res Hum Genet. 2006;9:849-857.

42. Derks EM, Dolan CV, Boomsma DI. Effects of censoring on parameter estimates and power in genetic modeling. Twin Res Hum Genet. 2004;7:659-669.

43. Neale MC, Boker SM, Maes H. Mx Statistical Modeling. 7 ed. Richmond, VA: Department of Psychiatry; 2006.

44. van Grootheest DS, Bartels M, van Beijsterveldt CEM, *et al.* Genetic and environmental contributions to self-report obsessive-compulsive symptoms in Dutch adolescents at ages 12, 14, and 16. J Am Acad Child Adolesc Psychiatry. 2008;47:1182-1188.

45. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291-303.

46. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13-23.

47. Kendler KS, Gardner CO, Annas P, Lichtenstein P. The development of fears from early adolesence to young adulthood: a multivariate study. Psychol Med. 2008;38:1759-1769.