Risk Factors for Childhood Problem Behavior: Studies in Twins and Triplets

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CHAPTER 2:

HERITABILITY OF ANXIOUS-DEPRESSIVE AND WITHDRAWN BEHAVIOR: AGE-RELATED CHANGES DURING ADOLESCENCE

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Abstract

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sample of 1470, 1839 and 2023 Dutch twins aged 12, 14 and 16 years reported on symptoms of anxious depression (AD) and withdrawn behavior (WB), using the Youth Self Report (YSR).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 non-shared (E) environment.

Results: The best-fitting models revealed no difference between heritability estimates in boys and girls. Familial clustering at age 12 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in agreement with earlier studies on age-specific effects of genes and shared environment on anxiety, depression and withdrawn behavior in childhood and adolescence.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.

Introduction

Anxiety disorders and depression are common disorders throughout the lifespan. Prevalence studies have established that between ages 5 and 17 around 8% of children suffers from an anxiety disorder. Nearly 5% in this age range suffers from major depression, but the prevalence tends to increase with age (peaking in adolescence)(Costello, Egger and Angold, 2005). 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 around 19% and 16%, respectively (Bijl, Ravelli and van Zessen, 1998; Kessler et al., 2005).

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 (see Rapee, Schniering and Hudson (2009) for a review). 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 (Rapee et al., 2009). Similar results hold for major depression, although the effects of childhood or adolescent depression seems to be more deleterious (Dunn and Goodyer, 2006; Pine, Cohen, Gurley, Brook and Ma, 1998). Co-morbidity within anxiety disorders and co-morbidity of anxiety disorders with depression is frequent in both children and adults (Angold, Costello and Erkanli, 1999; Brady and Kendall, 1992; Costello, Mustillo, Erkanli, Keeler and Angold, 2003; Ford, Goodman and Meltzer, 2003; Kessler, 1995). Research suggests that this may be due to common, mostly genetic, risk factors (Middeldorp, Cath, van Dyck and Boomsma, 2005).

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 (Rapee et al., 2009; Gregory and Eley, 2007; Hettema, Neale and Kendler, 2001; Rice, Harold and Thapar, 2002a; Rice, 2009; Sullivan, Neale and Kendler, 2000; Middeldorp and Boomsma, 2009).

Studies performed on 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 (Thapar and McGuffin, 1994; Feigon, Waldman, Levy and Hay, 2001; Kendler et al., 2008; Rice, Harold and Thapar, 2002b; Schmitz, Fulker and Mrazek, 1995; Scourfield et al., 2003). 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 (Bergen et al., 2007). 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 (Gjone, Stevenson, Sundet and Eilertsen, 1996). In addition, some studies have reported distinct changes in boys and girls, whereas other studies reported no clear changes at all (Legrand, Mcgue and Iacono, 1999; Eley and Stevenson, 1999; Silberg et al., 1999; Kendler, Gardner and Lichtenstein, 2008).

This inconsistency may be due to 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, the teacher, or the child itself). 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 (Rapee et al., 2009; Gregory and Eley, 2007; Rice et al., 2002a). In addition, estimates of shared environmental influences tend to be lower when based on parental ratings.

Another source of inconsistency may be the variation in the age range of the participants. Almost all of the 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 (Kendler et al., 2008; Gjone et al., 1996; Kendler et al., 2008; Legrand et al., 1999). 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 (Bartels et al., 2004; Hoekstra, Bartels, Hudziak, van Beijsterveldt and Boomsma, 2008; Boomsma, van Beijsterveldt and Hudziak, 2005). 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 (MZ) and dizygotic (DZ) 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; Achenbach and Rescorla, 2001), and are highly related to DSM-IV diagnoses of

anxiety disorders and depression (APA, 2000; Doyle, Mick and Biederman, 2007). 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, non-shared, environmental (E) factors on AD and WB. To address the issue of possible influence of raters on the outcomes, we compare results with those of the analyses of the parental reports on AD and WB for this sample at age 12 (Hoekstra et al., 2008; Boomsma et al., 2005).

Methods

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. 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 having ascertained parental informed consent, questionnaires were sent to the adolescent twins at ages 14 and 16 years. In addition to the ongoing data collection at the NTR, sub-samples 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 participated in a project on behavior problems, cognition, and hormones. 806 twins participated in a project on attention problems and hyperactivity, and 392 twins participated in a project on attention and executive functioning. (Bartels, 2002; Derks, 2006; Polderman et al., 2006). The 12-year olds that 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. (2007) and Boomsma et al. (2006).

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 3-point scale response format. The AD subscale comprises 16 items, with possible responses 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 7 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 of zero, standard deviation of one). 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 distributed data (Derks, Dolan and Boomsma, 2004).

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 within twin pairs within and across traits allowing differences between sexes and zygosity groups. We used the software package Mx to this end (Neale M.C., Boker S.M. and Maes, 2006).

Estimating correlations for MZ and DZ twin pairs constituted a first step towards 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 non-twin 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 non-shared 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 non-shared 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 factor loadings 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 breakdown 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 which 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 0.05 we concluded that the constraints associated with the more parsimonious model are tenable.

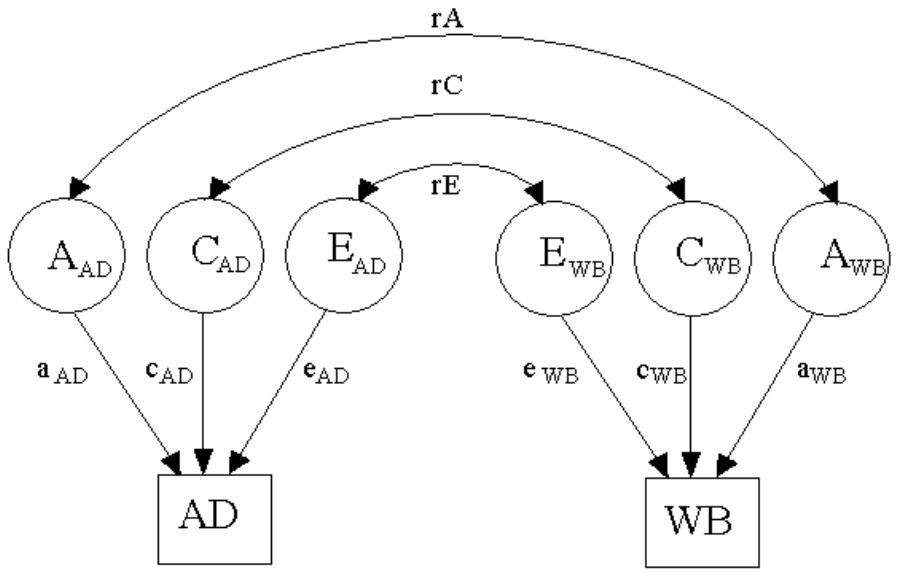

Figure 1: Path diagram of the bivariate genetic model. The observed variables are represented with a square (AD = anxious depressive, WB = withdrawn behavior), the latent factors by circles (A = additive genetic, C = shared environment, E = non-shared environment). The variance within an observed variable 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 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 environmental; E = nonshared environmental

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 1038 girls, and 903 boys and 1120 girls, 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 tend to increase with age. In view of these results, thresholds were estimated separately per age group 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 individual 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 ($\chi2(3) = 10.4$, $p = .02$, and $\chi2(3) = 20.6$, $p < .01$, respectively). This means that at age 12 both genetic and shared environmental effects 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 ($\chi2(3) = 0$, $p = 1.00$, and $\chi2(3) = 0.8$, $p = .84$). 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 non-shared environment, with the associated confidence intervals (CI).

The YSR AD and WB scales are highly correlated. This correlation is mostly explained by shared genes. The correlations between genetic factors are 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 1.0. Unique environmental factors were less correlated, with estimates around 0.5.

Table 1. *Twin correlation for the categorized anxious depressed and the 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 depressed; 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.

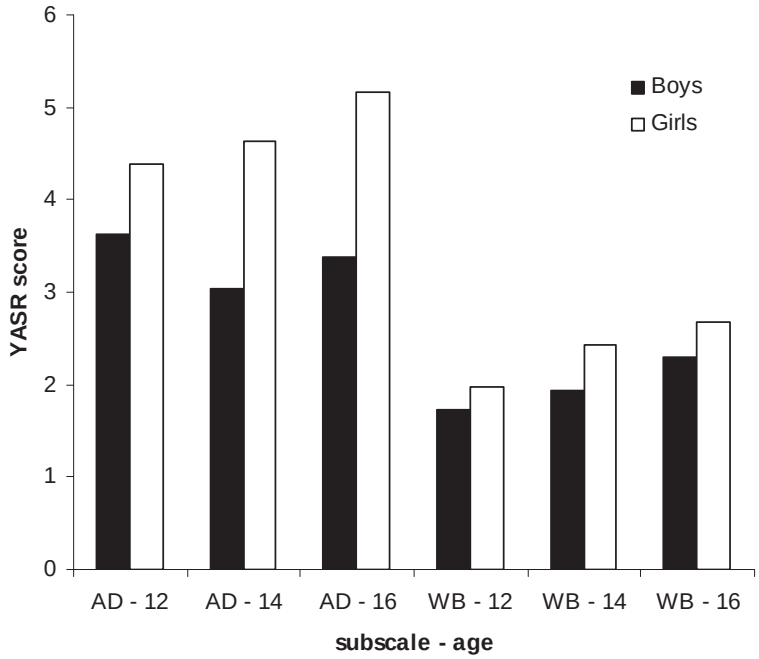

Figure 2: Mean scores on anxious depressed and withdrawn behavior as a function of sex and a

anxious depressed; WB = withdrawn behavior; YASR = Young Adult Self Report.

Table 2. *Model fitting results for the 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**	**1.00**	**-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	0.21	0.45	0.03	0.38	0.60	1.00	1.00	0.50
	(0.25 – 0.44)	(0.09 – 0.30)	(0.37 – 0.56)	(0.00 – 0.10)	(0.25 – 0.47)	(0.51 – 0.68)	(0.00 – 1.00)	(1.00 – 1.00)	(0.24 – 0.59)
14	0.67	-	0.33	0.37	-	0.63	0.85	-	0.42
	(0.46 – 0.72)		(0.26 – 0.41)	(0.18 – 0.47)		(0.53 – 0.68)	(0.75 – 0.97)		(0.30 – 0.48)
16	0.55	-	0.45	0.45	-	0.55	0.85	-	0.51
	(0.46 – 0.63)		(0.37 – 0.54)	(0.35 – 0.54)		(0.46 – 0.65)	(0.75 – 0.94)		(0.40 – 0.60)

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

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 play a role from age 12 to age 16, with estimates of explained variance around 0.4 for AD and around 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 (Feigon et al., 2001; Kendler et al., 2008; Rice et al., 2002b; Schmitz et al., 1995; Scourfield et al., 2003; Thapar and McGuffin, 1994).

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 (van Grootheest et al., 2008). 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 around 10% of the 12-year-old twins appeared to be in Tanner stage 1 (no pubic hair or breast development) (Marshall and Tanner, 1969; Marshall and Tanner, 1970). Thus, in 90% of the present 12-year-olds, puberty had already started. Another explanation is that the influence of C decreases due to a gradual attenuation of the level of parental control and time spent at home and together with the co-twin. 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 (Bartels et al., 2004; Hoekstra et al., 2008; Boomsma et al., 2005). Only with respect to WB was the present estimate of the effect of C higher than reported by Hoekstra et al., 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 (Rapee et al., 2009; Gregory and Eley, 2007; Rice et al., 2002a).

Discrepancies with results of other studies can be due to 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 (Eley and Stevenson, 1999; Silberg et al., 1999). However, this does not explain why Kendler et al. (2008) and Legrand et al. (1999) found no age differences in the es-

timates of A and C, whereas Gjone et al. (1996) found an increase in the effect of C with age. Kendler et al. did not actually test the effects of C by age, so they may have missed some effect. They also used parental reporting in addition to self-reporting. There is no clear explanation for the lack of age specific effects found by Legrand et al.. There is also no clear explanation for the effect of C at age 14 to 15 found by Gjone et al. in a Norwegian twin sample. However, at least compared to 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 (Feigon et al., 2001; Scourfield et al., 2003; Kendler et al., 2008; Eley and Stevenson, 1999; Silberg et al., 1999). This discrepancy might be due to differences in power and heterogeneity in phenotypes.

A limitation of the 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 (Kendler et al., 2008; Kendler et al., 2008; Kendler, Gardner, Annas and Lichtenstein, 2008). 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 suffer from anxiety and/or depression early in life, while others do not have any 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.