REVIEW

Genetic and Environmental Stability in Attention Problems Across the Lifespan: Evidence From the Netherlands Twin Register

Kees-Jan Kan, Ph.D., Conor V. Dolan, Ph.D., Michel G. Nivard, M.Sc., Christel M. Middeldorp, Ph.D., Catharina E.M. van Beijsterveldt, Ph.D., Gonneke Willemsen, Ph.D., Dorret I. Boomsma, Ph.D.

Objective: To review findings on attention-deficit/hyperactivity disorder and attention problems (AP) in children, adolescents, and adults, as established in the database of the Netherlands Twin Register and increase the understanding of stability in AP across the lifespan as a function of genetic and environmental influences. **Method:** A longitudinal model was fitted on Netherlands Twin Register AP scores from 44,607 child (<12-year-old), adolescent (12- to 18-year-old), and adult (>18-year-old) twins. **Results:** Mean AP showed a downward trend with age. Age-to-age correlations ranged from 0.33 (50–≥60 years old) to 0.73 (10–12 years old). Stability in individual differences in AP was due to genetic and environmental factors, and change was due primarily to environmental factors. Nonadditive genetic influences were present from childhood to adulthood. Total genetic variance decreased slightly throughout aging, whereas environmental variance increased substantially with the switch from maternal to self-ratings at 12 years of age. As a result, heritability coefficients decreased from 0.70 to 0.74 in childhood (maternal ratings) to 0.51 to 0.56 in adolescence (self-ratings), and 0.40 to 0.54 in adulthood (self-ratings). In childhood, male subjects scored higher than female subjects. After the rater switch at 12 years of age, female subjects tended to score higher than male subjects. **Conclusions:** Stability of AP is the result of genetic and environmental stability. The decrease in estimated heritability at 12 years of age is due to an increase in occasion-specific environmental variance and likely reflects a methodologic effect. Because environmental influences have lasting effects on AP, their early detection is crucial. J. Am. Acad. Child Adolesc. Psychiatry; 2012;52(1):12–25.
Key Words: attention problems, attention-deficit/hyperactivity disorder, heritability, genetic stability, rater effects

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity.[1] The prevalence of ADHD is highest in childhood, after which the number and the severity of its symptoms tend to decrease.[2] However, of the children who are diagnosed with ADHD, 15% retain this diagnosis by 25 years of age, whereas 50% are characterized by partial remission.[3] Notably, the decrease in ADHD symptoms tends to be more pronounced in hyperactivity and impulsivity than in inattention.[4] Taken together, these findings show that throughout development, ADHD and its symptoms demonstrate change, but also stability. Further support for stability in ADHD and ADHD symptoms can be found when considering individual differences in ADHD-related traits. Individual differences in attention problems (AP), for example, are moderately to highly stable over time.[5]

The aim of the present study was to increase the understanding of individual differences in AP and ADHD as a function of genetic and environmental effects and age. To this end, the authors summarize how the longitudinal database of the Netherlands Twin Register (NTR) has furthered the current understanding. Next, the authors elaborate on this line of research and investigate genetic and environmental stability and change in AP across the lifespan by fitting a longitudinal behavior genetic model to data from the NTR

This article is discussed in an editorial by Drs. James J. Hudziak and Douglas K. Novins on page 6.

database. These data were collected in 44,607 preadolescent (<12-year-old), adolescent (12- to 18-year-old), and adult (>18-year-old) twins over a period longer than two decades.

THE NTR: A LONGITUDINAL DATABASE

Recruitment and Data Collection

Previous NTR studies have been devoted to the description of the participants' recruitment, response rates, demography, and data collection.[6,7] Here, the authors provide a brief summary, followed by a review of the findings on the etiology of ADHD and AP, as established in the NTR database.

The NTR (http://www.tweelingenregister.org) has recruited newborn twins since 1987. Since then, about 40% of all Dutch newborn twins (and higher-order multiples) have been registered by their parents. These parents constitute the most important source of information during their children's early development (at 1, 2, 3, 5, 7, 10, and 12 years of age). When the twins turn 7, 10, and 12 years old, the parents are asked for permission to approach their children's teachers. At 14 and 16 years of age, the twins are asked to provide self-ratings. At this point, the siblings of the twins, if present, are invited to participate. Once the twins turn 18 years old, they, their siblings, and their parents enroll into the adult register and are invited to take part in ongoing studies.

In 1990, the NTR recruited, through city councils in the Netherlands, a large additional sample of adolescent and adult twins and their family members (parents, siblings, and spouses). Registration is ongoing. As of 2012, more than 35,000 twin pairs are enlisted with the NTR. Cross-sectional and longitudinal data have been collected by mailed surveys every 2 to 3 years, starting in 1991 (~22,000 participants from 5,546 families have taken part). Ongoing surveys 8 and 9 were initiated in 2009 and 2011, respectively. The registered twins are born in all strata of society, and the NTR participants are representative of the general population.[8] The NTR does not have exclusion criteria, mainly because the inclusion of special groups allows research in possible risk groups (such as children who are born at low birth weight or who are conceived with in vitro fertilization). Hence, all multiples and their family members are welcome to participate.

The data collected concern growth, health, cognition, and emotional and behavioral problems. Longitudinal measurements include variables relating to life events, demographics, lifestyle (exercise behavior, smoking, drinking, and other substance use), major medical illnesses, medication use, body mass index, personality, depression and anxiety, and variables related to ADHD. Subgroups of participants take part in projects that involve brain (EEG and magnetic resonance imaging) research, neuropsychological testing, psychiatric interviews, and cardiovascular studies. A large part of the adult participants has taken part in the NTR Biobank study.[9] Biological samples, which include DNA, RNA for expression profiling, cell lines, and multiple serum and plasma samples for biomarker studies, have been collected from about 10,000 adult subjects. DNA samples of children are also available. As part of the Genome of the Netherlands project, DNA sequence data have been assessed in 110 trios (parents and offspring) in 20 families consisting of parents and two twin offspring. Some individuals have provided multiple biological samples, which have been used to explore the longitudinal stability of DNA methylation.[10]

RESULTS CONCERNING ADHD AND AP

The NTR database has furthered the understanding of many aspects of various human biological and psychological traits, including healthy and pathologic outcomes of development. Table 1 presents the results of the NTR research into ADHD and AP.[11–32]

The findings most relevant to this study are the following. ADHD is more appropriately conceptualized as the extreme end of a continuum (or set of continuums) rather than a discrete category (or multiple discrete categories),[11] which is important theoretically. Although ADHD, ADHD symptoms, and AP are different phenotypes, their heritability estimates are of about the same magnitude. Moreover, ADHD, ADHD symptoms, and AP are, at least in childhood, affected by largely the same sets of genes.[12] However, the actual genes underlying these phenotypes remain unidentified.[13]

Heritability estimates of individual differences in ADHD symptoms and AP depend to some extent on rater and (to a lesser extent) on instrument. According to mother ratings on the Child Behavior Checklist (CBCL), AP are about 75% heritable,[14] whether AP are measured at 7, 10, or 12 years of age. Mother ratings on the Conners

TABLE 1 Results of Netherlands Twin Register (NTR) Research Into Attention-Deficit/Hyperactivity Disorder (ADHD), ADHD Symptoms, and ADHD-Related Traits

Study	Age (y)	(Sub)sample	Cohort(s) [or Wave(s)]	Ratings of ADHD, ADHD Symptoms, or ADHD Related Traits [Other Relevant Measurements]	Rater(s)	Results
[17]	3	9,689 twin pairs	1986–1997	CBCL OA	mother and father	h^2 OA 78%; no sex differences in heritability
[14]	3	11,938 twins	1986–1993	CBCL OA	mother	h^2 OA ~75%; AP ~75% at each age; genetic stability across development
	7	10,657 twins	1986–1993	CBCL AP	mother	
	10	6,192 twins	1986–1991	CBCL AP	mother	
	12	3,124 twins	1986–1989	CBCL AP	mother	
[13]	3, 7, 10, 12	16,169 twins in total, of whom 1,148 were genotyped	[2004–2005]	CBCL OA (3 y old) and CBCL AP (7–12 y old) [genotype, candidate genes]	mother and father	none of the candidate genes plays a role in development of AP
[23]	3, 7, 10, 12	13,371, 8,084, 5,367, 4,578 twin pairs	1986–2003	CBCL OA (3 y old) and CBCL AP (3, 10, 12 y old) [birth weight]	mother	AP shows shared etiology with low birth weight
[24]	3, 5, 7, 10, 12, 10-17	95 discordant MZ twin pairs in total	1986–1994	CBCL AP (3, 7, 10, 12 y old); TRF AP (7, 10, 12 y old); YSR AP (12 y old); SWAN (10–17 y old); DISC (10–17 y old)	mother; teacher; self; mother; medical students	evidence for environmental mediators
[18]	5	237 twin pairs	1990–1992	TRF AP	teacher	h^2 AP 63%
[15]	7	1,595 twin pairs	1992–1996	Conners ADHD index	mother	h^2 ADHD index 78%
[19]	7, 7	2,057, 2,259 twin pairs	1992–1996	CBCL AP; TRF AP	mother; teacher	h^2 common AP factor 78%; h^2 specific AP factors 76% (mother) and 39% (teacher)
[20]	7	1,651 twins	1992–1996	Conners ADHD index	teacher	h^2 ADHD index 56%–71%, no sex differences in heritability
[21]	7, 10, 12	25 MZ twin pairs in total	1986–1993	CBCL AP [structural imaging]	mother	genetic and environmental risk factors of AP affect brain volume in different ways
[25]	7, 10, 12	27 MZ twin pairs in total	1986–1993	CBCL AP [functional imaging]	mother	genetic and environmental risk factors of AP affect brain functioning in different ways

TABLE 1 Continued

Study	Age (y)	(Sub)sample	Cohort(s) [or Wave(s)]	Ratings of ADHD, ADHD Symptoms, or ADHD Related Traits [Other Relevant Measurements]	Rater(s)	Results
11	7, 10, 12	8,079, 5,278, 3,139 boys	—	CBCL AP	mother	ADHD is most appropriately conceptualized as lying on extreme end of continuum
11	12	489 boys		DISC	mother and interviewer	
26	7, 10, 12	19,150 twins and 2,600 singletons in total	1986–1998	CBCL AP	mother	AP trajectories of twins do not differ from those of singletons
27	7, 10, 12	50 MZ twin pairs discordant for ADHD	1986–1994	CBCL AP [CNVs]	mother	affected individuals have significantly larger CNVs than unaffected individuals
12	7	6,565 twins	1989–1994	CBCL AP	mother	h^2 AP 75%; h^2 ADHD index 84%; h^2 ADHD syndrome 65%; large genetic overlap among AP, ADHD index, and ADHD syndrome
	10	5,780 twins	1989–1994	CBCL AP	mother	
	12	4,887 twins	1989–1994	Conners ADHD index	mother	
	12	1,006 twins	1989–1994	ADHD syndrome	mother and research assistant	
28	9	112 twin pairs with siblings	1995–1996	CBCL AP	mother	association between AP and inhibitory control largely driven by genetic factors that also influence IQ
	12	177 twin pairs with siblings	1986–1989	[WISC; Stroop/ inhibitory control]		
	18	186 twin pairs with siblings	1986–1989			
16	12	562 twin pairs	1990–1992	CBCL AP; SWAN hyperactivity and attention deficit	mother	h^2 73% AP, h^2 90% hyperactivity, h^2 82%, attention deficit
29	12	354 twin pairs with siblings	1990–1992	SWAN [Amsterdam Neuropsychological Tasks, motor control]	mother	h^2 ADHD 75%; h^2 motor control 10%; no association between ADHD and motor control
		55 siblings of twin pairs	1986–1995			
30	18–30	4,245 twins	[1991, 1995, 1997]	YASR AP	self	h^2 AP 40%
22	>18	12,954 individuals	[2004–2005, 2008]	CAARS ADHD index	self	h^2 ADHD index 30%; evidence for assortative mating and genetic transmission; no evidence for cultural transmission

TABLE 1 Continued

Study	Age (y)	(Sub)sample	Cohort(s) [or Wave(s)]	Ratings of ADHD, ADHD Symptoms, or ADHD Related Traits [Other Relevant Measurements]	Rater(s)	Results
31	> 18	10,850 individuals	[2004–2005]	CAARS, inattention, hyperactivity, ADHD index	self	h^2 inattention 35%; h^2 hyperactivity 23%; h^2 ADHD-index 39%; associated QTL on chromosomes 18q and 2p
32	> 18	7,233 twins and siblings	[2004–2005]	CAARS ADHD index; [Personality Assessment Inventory, Borderline Features Scale]	self	h^2 ADHD index 35%; h^2 borderline 23%; phenotypic correlation between traits 0.59, genetic correlation 0.72, environmental correlation 0.52

Note: AP = attention problems; CAARS = Conner Adult ADHD Rating Scales; CBCL = Child Behavior Checklist; CNV = contingent negative variation; DISC = Diagnostic Interview Schedule for Children; h^2 = heritability; MZ = monozygotic; OA = overactivity; QTL = quantitative trait locus; SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale; TRF = Teacher Report Form; (Y)ASR = (Young) Adult Self-Report.

ADHD Rating Scales and the Strengths and Weaknesses of ADHD Symptoms and Normal Behaviors Questionnaire yield very similar results (i.e., heritability of 78%–82% at 7 years of age).[15,16] Although parents may have unique views on the children's behavior, heritability estimates of AP based on mother ratings (on the CBCL) do not differ from those based on father ratings (on the same scale, at the same age).[17]

The existence of rater-specific views may explain why heritability estimates of AP based on teacher ratings are overall somewhat lower, around 55% to 63%.[18,19] Each parent usually rates the behavior of both twins, but a substantial number of twin pairs is rated by different teachers rather than the same teacher. Intercorrelations between ratings are expected to be lower when different rather than the same informants provide the ratings.[19]

The use of multiple informants is recommended in the assessment of ADHD.[19] Despite having specific views or evoking specific behaviors, different informants appear to rate a common ADHD-related phenotype. This common phenotype is a good predictor of ADHD. Its heritability estimate is high, around 78%. The specific views provide valuable additional information about the subject's problems.

The NTR research has shown that the environmental effects on ADHD and AP constitute unique environmental effects rather than shared environmental effects. Shared environmental influences appear to be absent, because dizygotic (DZ) twin correlations of ADHD and AP are generally more than twice as low as monozygotic (MZ) twin correlations. Appreciable difference between MZ and DZ correlations is suggestive of nonadditive genetic effects, such as dominance or epistasis. An alternative or additional explanation is the presence of a (negative) sibling interaction effect.[33] This means that the higher the one twin scores, the lower the other twin scores. Whether such an effect reflects interactions between twins on the behavioral level or reflects a rater effect or "bias" has not been clarified.

Of particular interest are the NTR results that provide insight into *how* genes have their influence. For example, AP appear to be affected by the same set of genes in girls and boys and appear to be equally heritable between sexes.[14,17,20] However, there are sex differences in means, i.e., boys have higher AP scores on average than girls.[20] Another finding is that

genetic influences affect the brain in different ways than environmental influences.[21,25] This is consistent with the finding that in models in which the pathways of genetic and environmental influences on AP and ADHD are considered to be independent fit better than common pathway models.[12]

Increasing Focus on Longitudinal Studies

The NTR has focused increasingly on longitudinal studies.[34] Longitudinal research is needed to advance the knowledge regarding causes of stability and changes in complex human phenotypes. For example, despite advances in ADHD and AP research, little is known about the role of genetic and environmental influences on the development of ADHD and AP from childhood to adulthood.

It is clear that genetic and environmental influences on a given phenotype can vary considerably throughout development. This implies that heritability coefficients of ADHD, ADHD symptoms, and ADHD-related traits, such as AP, can vary across ages. Indeed, a recent NTR study in more than 12,000 adults has suggested that heritability of ADHD symptoms decreases from childhood to adulthood.[22] In this study, the estimated heritability of individual differences in scores on the CAARS was around 30%, which is considerably lower than estimated heritability of related traits obtained from child samples.[14,37] The results of this study also suggested that genetic changes are present during development. In the adult sample, nonadditive genetic effects on the CAARS scores appeared to be absent,[22] whereas in child samples nonadditive genetic effects have been reported in several related variables.[35] Hence, the difference in the estimated heritability of ADHD-related variables between the adult and child samples may be due to a decrease in nonadditive genetic effects during development.

In addition to evidence for genetic change, there is evidence for genetic stability during the course of development. Longitudinal NTR studies have shown that a subset of the genes that give rise to individual differences in AP earlier in childhood (e.g., at 7 years of age) also influence AP later in childhood (e.g., at 10 years of age),[14] and those that influence AP in young adulthood (e.g., at 18 years of age) influence AP later in adulthood (e.g., at 30 years of age).[30]

GENETIC AND ENVIRONMENTAL STABILITY AND CHANGE IN ATTENTION PROBLEMS ACROSS THE LIFESPAN

The present study builds on previous work by investigating the extent to which the same and different genetic and environmental influences affect AP throughout the lifespan. To this end, the authors combine measurements of AP from preadolescent, adolescent, and adult twins who were recruited by the NTR. Next, they analyze the combined data using a longitudinal behavior genetic model. The report ends with a discussion of the results.

METHOD

Sample

The sample was comprised of 44,607 twin members who participated in longitudinal NTR projects[34] and who took part on at least one measurement occasion. Of 26,050 twin pairs, sufficient information was available to determine their zygosity, which was obtained from DNA polymorphisms (7.97%) or from well-validated questions or opposite-sex information. The 3,982 MZ male, 5,178 MZ female, 4,280 DZ male, 4,294 DZ female, and 8,316 DZ opposite-sex pairs had an age range of 3 to 90 years. The numbers of individuals who participated at one to eight occasions were 19,322, 8,699, 5,406, 4,820, 3,321, 2,247, 667, and 125. Around 17% of the twins participated without their cotwins ever participating.

Instruments and Protocol

Assessment of AP was based on the AP scales of the Achenbach System of Empirically Based Assesment.[36] The behavior of children ($\leq$12 years old) was rated using the CBCL, that of adolescents (12–18 years old) was rated using the Youth Self-Report/11-18 (YSR), and that of adults (>18 years old) was rated using the Adult Self-Report (ASR) or an adapted version of the YSR. Overall ratings rather than specific item scores were analyzed. The authors assumed that the CBCL, YSR, and ASR AP scores estimate the level of AP, although the questions on the CBCL, YSR, and ASR do not overlap completely, and while most AP items are more related to ADHD symptoms of inattention, others are more related to hyperactivity and impulsivity or are not specific to the official diagnostic criteria of ADHD. Mean values of the item scores were calculated. These were comparable across scales, because all items were scored on a 3-point scale (0, not true; 1, somewhat or sometimes true; or 2, very true or often true).

In children and adolescents, data were collected when the twins reached 3, 7, 10, 12, 14, and 16 years of age (see the description of NTR data collection above). Afterward, the twins enrolled in the NTR adult data

TABLE 2 Structure of the Young Netherlands Twin Register (YNTR) and Adult Netherlands Twin Register (ANTR) Data Related to Attention Problems (AP), Number of Monozygotic (MZ) and Dizygotic (DZ) Twin Pairs in Each Age Category (n), and Twin Pair Correlations (r)

Database	YNTR			Mix of YNTR and ANTR		ANTR								
Rater	Mother					Self								
Instrument	CBCL			YSR		ASR or adapted YSR								
Scale	OA	AP												
Age category	3	7	10	12	13–15	15–17	17–19	19–21	21–23	23–25	25–30	30–40	40–50	50–60	≥60
n MZ	5,317	3,522	2,539	2,447	314	931	1,312	1,105	652	388	227	245	502	235	184	125
n DZ	10,786	6,531	4,429	4,154	439	1,444	1,963	1,554	878	558	324	281	505	163	126	87
r MZ	0.698	0.718	0.724	0.703	0.576	0.536	0.493	0.483	0.537	0.439	0.427	0.390	0.531	0.488	0.517	0.447
r DZ	0.177	0.239	0.229	0.237	0.215	0.195	0.214	0.215	0.205	0.170	0.133	0.193	0.164	0.266	0.194	0.105

Note: At age 3 AP is approximated by overactivity (OA). ASR = Adult SelfReport; CBCL = Child Behavior Checklist; YSR = Youth SelfReport.

collection. In adults, data were collected in NTR surveys 1 (1991), 3 (1995), 4 (1997), 5 (2000), and 8 (collection started in 2009). The YSR was included in surveys 1, 3, 4, and 5 and is currently included in all surveys sent to 14- and 16-year-olds. The ASR was included in survey 8. Although the ASR was designed for subjects 18 to 65 years old, older participants were invited to complete it. More information about the data collection is detailed elsewhere.[6,7]

In 753 twin pairs 12 years of age, self-ratings were available. To distinguish between the effects of genetic or environmental innovations at 12 years of age, on the one hand, and the effects of the switch in raters, on the other, these ratings were included as a separate variable.

Also included were mother ratings on the CBCL Overactivity (OA) scale of 3-year-olds (AP scores at 3 years of age were not available). Notwithstanding the distinction between OA and AP, the OA score was as a rough proxy of AP at 3 years of age and as an informative predictor of AP at 7 years of age.[14]

Reorganization of the Data

The data required reorganization according to age. Children, adolescents, and young adults were better represented than the middle-aged and elderly, so that relatively broad age categories had to be constructed in older age to have a sufficient number of observations in each cell to carry out statistical analyses. The following age categories were created: 3, 7, 10, and 12 years, covering mother ratings of AP (OA at 3 years); and 12, 13 to 15, 15 to 17, 17 to 19, 19 to 21, 21 to 23, 23 to 25, 25 to 30, 30 to 40, 40 to 50, 50 to 60, at least 60 years, covering self-ratings of AP.

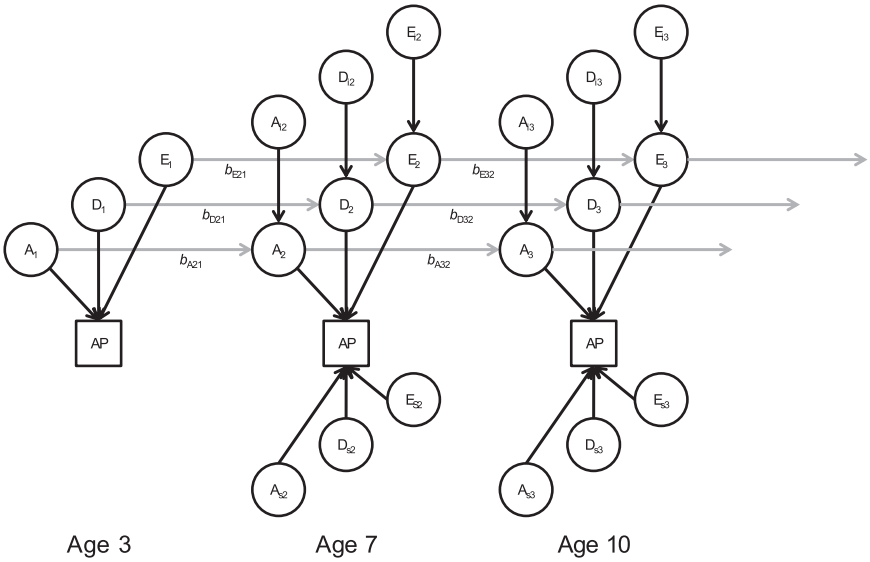
Statistical Analyses

Descriptive Statistics. Table 2 presents the number of twin pairs within each age category. The last two rows present twin pair correlations. These correlations show that at each age the MZ twins resemble each other in AP to a greater extent than same-aged DZ twins, implying genetic effects on AP across all ages. Age-to-age correlations in AP ranged from 0.33 (50–≥60 years old) to 0.73 (10–12), reflecting moderate to high stability of individual differences in AP.

Longitudinal Modeling. From age category to age category, longitudinal data were always present, implying that the variable AP within a certain age category can be regressed on AP within the previous age category. This means that using the raw data to fit the longitudinal model, the expected covariance between, for example, OA at 3 years or AP at 7 years and AP at 60 years and older, can be derived, although no individuals were followed during such a long period.

The total variance in AP (OA at 3 years of age) within each age category was decomposed into genetic and environmental variance components.[37] This is possible in a twin design, because MZ twins share (nearly) 100%

FIGURE 1 Longitudinal behavior genetic model ("genetic simplex"). Note: Additive genetic (A), nonadditive genetic (D), and environmental latent factors explain the variance in attention problems (AP) at several measurement occasions (1, 2, 3, …), here at 3, 7, 10 years, and older (see text). The genetic (environmental) variance at a certain measurement occasion is to some extent explained by the genetic (environmental) variables at the previous measurement occasion. New genetic (environmental) variance arises due to innovations (i) whose effects are transmitted to the next measurement occasion and to measurement occasion-specific influences (s) whose effects are not transmitted and are thus transient.



of their genetic material, whereas DZ twins share (on average) 50% of segregating genes. Genetic variance was further decomposed into additive genetic variance and nonadditive genetic variance, rather than environmental variance into unique environmental variance and shared environmental variance, because previous studies (NTR[35] and non-NTR[38,39]) have suggested that shared environmental variance components do not account for any significant amount of variance in AP at any age and MZ correlations were generally more than twice as high as the DZ correlations (Table 2), which is generally interpreted as evidence for effects of nonadditive genetic influences (but see the Discussion).[40] Sex was included as a predictor of the observed variables to allow for mean sex differences in AP.

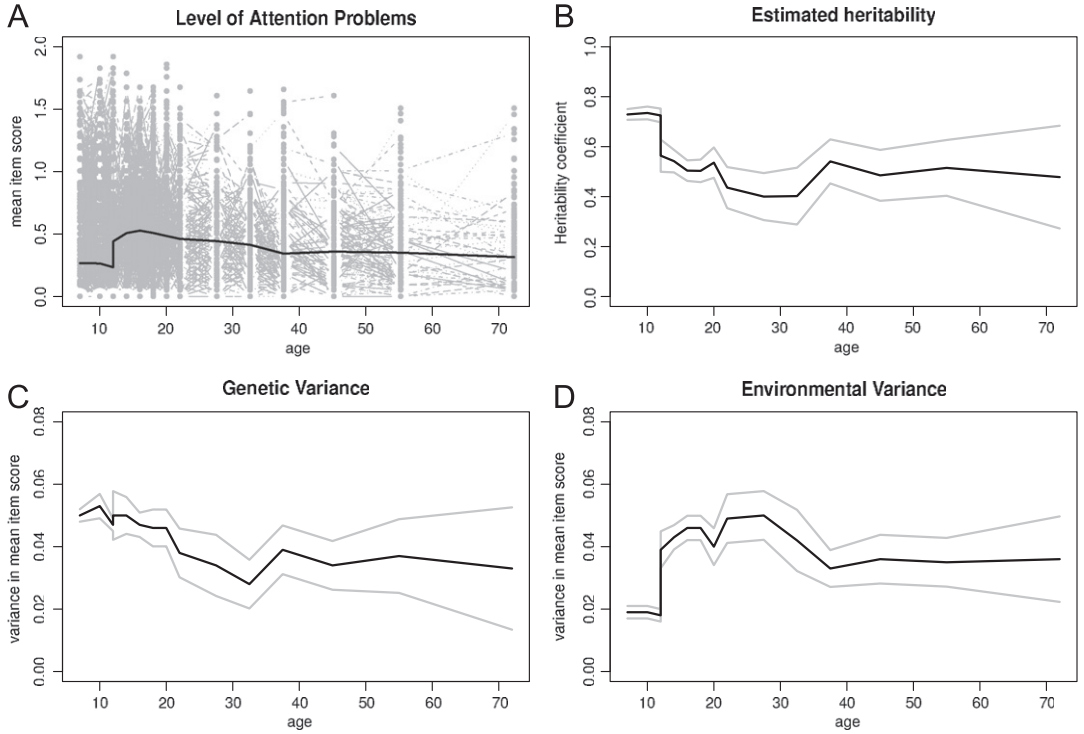
In accordance with the method advanced to study longitudinal twin data,[41] the authors fitted a "genetic simplex model."[42] Genetic simplex models are models that include first-order autoregressions between the subsequent genetic (and environmental) factors, i.e., regressions in which genetic (environmental) variance at a certain measurement occasion is explained by genetic (environmental) variables at the previous measurement occasion (Figure 1). In such models, genetic (environmental) correlations are highest among adjoining measurement occasions and become smaller as the time between two measurement occasions increases.

Genetic simplex models allow for the distinction between variance owing to so-called genetic (environmental) innovations, on the one hand, and variance owing to measurement occasion-specific genetic (environmental) influences, on the other. What innovations and measurement occasion-specific influences have in common is that they comprise influences that explain parts of the variance in the observed variable at the current measurement that is not explained by the variables at the previous measurement occasion. They differ in that innovations explain part of the variance in the variables at later measurement occasions, whereas occasion-specific influences do not. In other words, the effects of innovations are carried over (transmitted) from the one measurement occasion to the next, whereas occasion-specific influences are not and are thus transient.

RESULTS

Table 3 presents the results of the longitudinal modeling. It contains the variances in the latent genetic and environmental variables and the autoregression coefficients between (and explained variance in) those variables. It also contains the variances of innovative and measurement-specific influences, the estimated means of AP, and the mean sex effects. Figure 2A shows the individuals' and the sample's mean item scores plotted against age. Figure 2B shows the broad-sense heritability coefficients (i.e., the proportions of phenotypic variance owing to [additive and nonadditive]

FIGURE 2 (A) Individual mean item scores (gray dots and dotted lines) on the Attention Problems (AP) scale throughout aging and the sample's overall average (black, solid line). Note: The data show longitudinal coverage from age category to age category; each line segment represents an individual. This allows the fit for the genetic simplex model shown in Figure 1. (B) Heritability estimates (black) of AP throughout aging, which were derived from fitting this model (95% confidence intervals in gray). (C) Genetic variance in mean items scores on AP (black) throughout aging (95% confidence intervals in gray). (D) Environmental variance in mean items scores on AP (black) throughout aging (95% confidence intervals in gray).



genetic effects; h^2) across age. These were derived from the estimates of the total (i.e., additive + nonadditive) genetic variance (Figure 2C) and environmental variance (Figure 2D).[37]

Stability and Changes in Genetic and Environmental Influences

The regression coefficients listed in Table 3 show that, in general, environmental and genetic influences are transmitted from measurement occasion to measurement occasion. Only from 50 to at least 60 years of age did the transmission of environmental effects approach zero (and the regression coefficient had to be constrained to avoid identification problems in the modeling). Nonadditive genetic effects were present from childhood to adulthood, although at certain measurement occasions the standard errors (SEs) of the parameters were large, resulting in statistical insignificance. Over the age categories, the degree of transmission, as expressed in the autoregressive coefficients, varied: sometimes regression coefficients were largest for environmental effects, sometimes for additive genetic effects, but most often for nonadditive genetic effects. Variances in innovative and occasion-specific environmental influences were generally significant, whereas their genetic counterparts were not (especially not after adolescence).

Changes in Estimated Heritability and Genetic and Environmental Variance

The h^2 of OA at age 3 was 0.704 (SE = 0.09), demonstrating the high heritability of OA. Before age 12, the h^2 of AP ranged from 0.725 (SE = 0.014) to 0.735 (SE = 0.013), demonstrating equally high heritability of AP in childhood. After age 12, heritability estimates of AP were lower. The h^2 of AP ranged from 0.503 (SE = 0.023) to 0.564 (SE = 0.033) in adolescence and from 0.400 (SE = 0.048) to 0.541 (SE = 0.045) in adulthood. At age 12, self-rated AP (AP-s) was less heritable ($h^2 = 0.564$, SE = 0.033) than mother-rated AP (AP-m; $h^2 = 0.725$, SE = 0.09). In general, AP-s was less heritable than AP-m. This can be observed from Figure 2B,

where the 95% confidence intervals of h^2 for AP-s and AP-m do not overlap. There was no significant negative trend in the heritability of AP (or AP-s).

At age 12, the genetic variance in AP-s (0.50, SE = 0.004) was not less than the genetic variance in AP-m (0.47, SE = 0.001), whereas the environmental variance in AP-s was 0.039 (SE = 0.003) and about twice as much as in the environmental variance in AP-m (0.018, SE = 0.001). This difference was significant. The difference in heritability between AP-s and AP-m at age 12 is thus due to a difference in environmental variance. In general, the environmental variance was larger in AP-s than in AP-m. This can be observed from Figure 2C, where the confidence intervals of environmental variance in AP-s and AP-m do not overlap. As can be gathered from Table 3, the increase in environmental variance constitutes mainly an increase in the variance of measurement-specific environmental influences, rather than an increase in variance of environmental innovations.

Apart from the increase in environmental variance, which coincided with the switch in rater, there was little change in the amount of genetic and environmental variance across age. For example, there was no significant trend in the amount of environmental, additive genetic, or nonadditive variance in AP (or AP-s). The amount of total genetic variance showed a trend: The Spearman rank correlation between age and total genetic variance in AP was −0.89 (S = 1,063.101, $p < .001$) and between age and AP-s this was −0.85 (S = 528, $p < .001$).

Changes in Mean AP and Sex Effects

There was a significant negative trend in the (sample) mean of AP-s: the Spearman rank correlation between age and the estimated (sample) mean of AP-s was −0.87 (S = 534, $p < .001$). In children, the mean AP-m of male subjects was higher than that of female subjects (Table 3). This was also the case at age 12, but according to the 12-years-olds the mean difference was smaller and insignificant. From 12 to 22 years of age, self-ratings showed a reversed sex effect: on average female subjects scored higher than male subjects. After age 22, sex differences in mean AP were generally not significant.

DISCUSSION

Building on previous NTR research, the authors aimed to further their understanding of the etiology of AP and ADHD as a function of genetic and environmental effects and age by investigating empirically the extent to which the same and different genetic and environmental influences affect AP throughout the lifespan. They also explored changes in mean AP and sex effects.

In general, genetic and environmental influences accounted for the stability of individual differences in AP. The notable exception was late adulthood (≥50 years old), when stability decreased due to instability in environmental effects. However, here the genetic effects remained a source of stability. Although environmental innovations were clearly present across all ages, genetic innovations were present less often before adulthood and largely absent in adulthood. That environmental innovations were ubiquitous suggests an accumulation of different lasting environmental effects on AP. Therefore, although the short-term prediction of AP is possible, the long-term prediction is difficult. The prediction of an individual's future level of AP will improve if environmental risk factors are identified, monitored, and taken into account.

The present results are largely in line with previous findings on the heritability of ADHD and related variables, including AP.[14,22,43–45] The estimated heritability of AP was high in childhood but only moderate in adolescence and adulthood. The main cause of this difference was an increase of (mainly occasion-specific) environmental variance at age 12, which coincided with the switch from mother ratings to self-ratings and, hence, with the switch from same rater (the mother who rates both twin members) to different raters (the twin members who rate themselves). The decrease in estimated heritability in AP is likely due to an increase in rater-specific variance. Such differences in heritability and specific variance have been found previously in children who were rated by the same teacher versus children who were rated by a different teacher.[19,46]

Consistent with the decrease in ADHD symptoms throughout development,[2] AP-s decreased on average throughout aging. With respect to sex differences in AP, the authors conclude that in childhood (until 12 years of age) the male subjects' mean rating of AP was greater than the female subjects' mean rating, whereas in late adolescence and young adulthood (15 to 30 years of age) the female subjects' mean rating of AP was greater than the male subjects' mean rating. In the 12-year-olds, the sex effects were present only in mean mother ratings and not in mean self-ratings. This finding supports the notion that rater effects are present.

TABLE 3 Results From the Longitudinal Model Fit

Trait	Age Category	A	D	E	A_i	D_i	E_i	A_s
OA-m	3	0.010* (0.003)	0.121* (0.004)	0.055* (0.002)				
AP-m	7	0.011* (0.003)	0.028* (0.003)*	0.011* (0.002)	0.000 (0.000)	0.021* (0.002)	0.010* (0.002)	0.011* (0.001)
AP-m	10	0.018* (0.005)	0.028* (0.005)	0.013* (0.001)	0.000 (0.000)	0.006* (0.001)	0.005* (0.001)	0.002 (0.003)
AP-m	12[a]	0.017* (0.004)	0.030* (0.004)	0.018* (0.001)	0.011* (0.003)	0.002 (0.003)	0.009* (0.001)	0.000 (0.000)
AP-s	12[a]	0.015 (0.012)	0.033* (0.008)	0.009* (0.004)	0.013 (0.012)	0.000 (0.000)	0.008* (0.004)	0.002 (0.014)
AP-s	13–15	0.020* (0.009)	0.024* (0.009)	0.019* (0.006)	0.013 (0.010)	0.007 (0.009)	0.009 (0.006)	0.001 (0.009)
AP-s	15–17	0.018* (0.006)	0.023* (0.006)	0.022* (0.005)	0.000 (0.000)	0.011* (0.004)	0.010* (0.005)	0.006 (0.004)
AP-s	17–19	0.032* (0.005)	0.014* (0.005)	0.028* (0.006)	0.016* (0.003)	0.000 (0.000)	0.011 (0.006)	0.000 (0.000)
AP-s	19–21	0.017 (0.009)	0.028* (0.010)	0.012* (0.003)	0.002 (0.007)	0.006 (0.009)	0.002 (0.003)	0.001 (0.004)
AP-s	21–23	0.011 (0.008)	0.018 (0.010)	0.032* (0.008)	0.004 (0.003)	0.000 (0.000)	0.016* (0.007)	0.004 (0.010)
AP-s	23–25	0.022* (0.008)	0.012 (0.008)	0.025* (0.007)	0.000 (0.000)	0.000 (0.000)	0.002 (0.006)	0.000 (0.000)
AP-s	25–30	0.003 (0.004)	0.025* (0.006)	0.036* (0.006)	0.001 (0.002)	0.000 (0.002)	0.018* (0.007)	0.000 (0.000)
AP-s	30–40	0.028* (0.007)	0.011 (0.006)	0.005* (0.002)	0.000 (0.000)	0.000 (0.000)	0.000* (0.000)	0.000 (0.000)
AP-s	40–50	0.005 (0.006)	0.018* (0.008)	0.036* (0.004)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.011* (0.004)
AP-s	50–60	0.017 (0.013)	0.020 (0.013)	0.035* (0.004)	0.000 (0.000)	0.000 (0.000)	0.035* (0.004)	0.000 (0.000)
AP-s	≥60	0.000 (0.003)	0.033* (0.009)	0.036* (0.007)	0.000 (0.000)	0.000 (0.000)	0.036* (0.007)	—

Note: The values represent variances, regression coefficients, or means. In general the values thus represent 'the parameter estimates.' % = percentage of variance in the latent genetic (or environmental) factors explained by the latent genetic (environmental) factor at the previous measured occasion; A = total additive genetic variance; AP = score on Attention Problems scale; AP-m = mother ratings of attention problems; AP-s = self-ratings of attention problems; b = autoregression coefficients between latent factors (Figure 1); D = total nonadditive genetic variance; E = total environmental variance; i = contribution of innovations; OA-m = mother ratings of overactivity; s = contribution of occasion-specific influences; sex = effect of sex (0 = male, 1 = female) on the mean.

[a]*A, D, and E factors at age 12 were regressed on A, D, and E factors at age 10.*

**Significant at* $\alpha = 0.05$.

Future research into rater effects or other methodologic effects is warranted. The diagnostic relevance is clear. That female subjects are rated as experiencing fewer problems than male subjects in childhood (according to mothers), although female subjects experience more problems than male subjects in adolescence (according to these subjects), may signify underdetection of the female subjects' problems. Such underdetection, which has been noted in the literature,[20] is obviously undesirable. Alternatively, the observed sex differences can signify that (adolescent) male subjects with AP tend to underestimate their problems. Evidence for this also has been reported.[47]

The presence of methodologic effects may explain why in previous research[22] nonadditive genetic effects in AP in adults were not detected, although these were detected in the present study. The switch from the same rater (one mother) in childhood to different raters (two twins) in adolescence and adulthood coincides with an increase in measurement-specific environmental

TABLE 3 Continued

D_s	E_s	b_A	%A	b_D	%D	b_E	%E	Mean	Sex
								0.528	−0.087* (0.005)
0.000 (0.000)	0.008* (0.002)	1.030* (0.113)	100	0.240* (0.019)	25	0.092* (0.013)	4	0.262	−0.088* (0.004)
0.005* (0.003)	0.006* (0.001)	1.267* (0.117)	100	0.878* (0.058)	77	0.856* (0.133)	59	0.264	−0.098* (0.004)
0.000 (0.000)	0.000 (0.000)	0.571* (0.084)	34	0.996* (0.061)	92	0.821* (0.048)	50	0.237	−0.092* (0.004)
0.000 (0.000)	0.029* (0.004)	−0.285 (0.321)	10	1.085* (0.146)	100	0.330* (0.089)	15	0.441	−0.006 (0.015)
0.005 (0.010)	0.024* (0.006)	0.711 (0.502)	37	0.706* (0.086)	69	1.010* (0.346)	52	0.516	0.023* (0.009)
0.000 (0.000)	0.024* (0.005)	0.951*; (0.193)	100	0.719* (0.077)	53	0.798* (0.225)	53	0.539	0.057* (0.007)
0.000 (0.000)	0.017* (0.006)	0.937* (0.163)	49	0.771* (0.097)	100	0.875* (0.203)	60	0.520	0.050* (0.008)
0.000 (0.000)	0.028* (0.003)	0.682* (0.103)	88	1.272* (0.224)	79	0.580* (0.129)	82	0.492	0.065* (0.010)
0.005 (0.012)	0.017* (0.007)	0.639* (0.192)	61	0.794* (0.155)	100	1.201* (0.241)	52	0.456	0.039* (0.013)
0.000 (0.000)	0.025* (0.005)	1.383* (0.338)	100	0.806* (0.186)	100	0.852* (0.165)	93	0.440	0.031 (0.016)
0.000 (0.000)	0.007* (0.003)	0.296 (0.193)	61	1.474* (0.476)	100	0.840* (0.172)	50	0.414	0.032 (0.016)
0.000 (0.000)	0.029* (0.003)	3.007 (1.842)	100	0.650* (0.173)	100	0.359* (0.098)	100	0.340	0.020 (0.014)
0.000 (0.000)	0.000 (0.000)	0.405 (0.229)	100	1.307* (0.409)	100	2.797* (0.716)	100	0.341	0.013 (0.023)
0.000 (0.000)	0.000 (0.000)	1.921 (1.256)	100	1.045* (0.374)	100	0.056 (0.137)	0	0.319	0.066* (0.025)
—	—	0.157 (0.659)	98	1.282* (0.501)	100	0.000 (—)	0	0.307	0.029 (0.030)

variance. High correlations (MZ correlations) may be affected relatively more by such increase than low or moderate correlations (DZ correlations). If so, the switch from maternal ratings to self-ratings is accompanied by relatively large decrease in MZ similarity compared with the decrease in DZ similarity. If effects of measurement-specific influences are not taken into account, a behavioral-genetic decomposition of the variance may suggest that the effects of nonadditive genetic influences decrease. The present longitudinal model took measurement-specific variance into account, so the authors were better able to detect nonadditive genetic effects. Whether nonadditive genetic effects are really present is still unclear. The authors did not consider alternative explanations such as sibling interaction, which imply differences in variances among family members as a function of zygosity and the number of siblings in the family. Such methods need to be developed to test for social interaction in longitudinal designs. Cross-sectional data analyses thus far have indicated sibling interaction to be of importance for AP.[33]

By considering the underlying causes of stability in AP throughout the lifespan, the authors hope to have contributed to the understanding of the etiology and persistence of AP throughout development. On average, AP may tend to decrease throughout development, but the individual differences therein are quite stable. Genetic and environmental influences have lasting effects on AP, but although the genetic effects arise early in development and do not change, the environmental effects

keep accumulating throughout life, thereby altering individual differences in AP. The same likely holds for ADHD. To prevent people from developing lasting AP or ADHD, the early detection of environmental influences and interventions taking into account these influences are crucial. &

Accepted October 16, 2012.

Drs. Kan, Dolan, Middeldorp, van Beijsterveldt, Willemsen, and Boomsma, and Ms. Nivard are with the Vrije Universiteit (VU) Amsterdam, the Netherlands. Dr. Dolan is also with the University of Amsterdam. Dr. Middeldorp is also with GGZ inGeest-VU Medical Center and the Amsterdam Medical Center. Dr. Boomsma is also with the Neuroscience Campus Amsterdam.

This research was supported by the following grants: genetic influences on stability and change in psychopathology from childhood to young adulthood (the Netherlands Organization for Health Research and Development grant 91210020), genetics of mental illness (European Research Council grant 230374), and genomics of developmental trajectories in twins (National Institute of Mental Health grant 1RC2MH08999501). This research was also supported by the Neuroscience Campus Amsterdam.

Drs. Kan and Dolan, and Ms. Nivard served as the statistical experts for this research.

This article is part of a special series on recent findings and progress in the fields of birth cohort and longitudinal studies of child and adolescent psychopathology. This special series is intended to showcase some of the most important new findings and promising leads in the study of developmental psychopathology over time and to demonstrate the *Journal*'s renewed commitment to publishing the highest quality articles on the topic. Each article is in part a review of the most important findings to date from the study and in part original research to allow readers to learn about a new research finding with a more complete context of the study than is usually possible.

Disclosure: Dr. Middeldorp was supported by a Veni grant from the National Organization for Scientific Research. Drs. Kan, Dolan, van Beijsterveldt, Willemsen, and Boomsma, and Ms. Nivard report no biomedical financial interests or potential conflicts of interests.

Correspondence to Kees-Jan Kan, Ph.D., Department of Biological Psychology, VU University Amsterdam, van der Boechorststraat 1, 1081 BT Amsterdam, the Netherlands; e-mail: k.j.kan@vu.nl

http://dx.doi.org/10.1016/j.jaac.2012.10.009

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed rev. Washington, DC: American Psychiatric Association; 2000.
2. Costello EJ, Copeland W, Angold A. Trends in psychopathology across the adolescent years: what changes when children become adolescents, and when adolescents become adults? J Child Psychol Psychiatry. 2011;52:1015-1025.
3. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med. 2006;36:159-165.
4. Biederman J, Mick E, Faraone SV. Age dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. 2000; 157:816-818.
5. Achenbach TM, Dumenci L, Rescorla AL. Are American children's problems still getting worse? A 23-year comparison J Clin Child Adolesc Psychology. 2003;31:1-11.
6. 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.
7. Boomsma DI, Willemsen AHM, Sullivan PF, *et al*. Genome-wide association of major depression: description of samples for the GAIN Major Depressive Disorder study: NTR and NESDA Biobank Projects. Eur J Hum Genet. 2008;16:335-342.
8. Bartels M, Hudziak JJ, 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.
9. Willemsen AHM, de Geus EJC, Bartels M, *et al*. The Netherlands Twin Register Biobank; a resource for genetic epidemiological studies. Twin Res Hum Genet. 2010;13:231-245.
10. Talens RP, Boomsma DI, Tobi EW, *et al*. Variation, patterns, and temporal stability of DNA methylation: considerations for epigenetic epidemiology. Fed Am Soc Exp Biol J.. 2010;24:3135-3144.
11. Lubke GH, Hudziak JJ, Derks EM, van Beijsterveldt TC, Boomsma DI. Maternal ratings of attention problems in ADHD: evidence for the existence of a continuum. J Am Acad Child Adolesc Psychiatry. 2009;48:1085-1093.
12. Derks EM, Hudziak JJ, Dolan CV, van Beijsterveldt TC, Verhulst FC, Boomsma DI. Genetic and environmental influences on the relation between attention problems and attention-deficit hyperactivity disorder. Behav Genet. 2008;38:11-23.
13. van Beijsterveldt CEM, Middeldorp CM, Slof-Op't Landt MC, *et al*. Influence of candidate genes on attention problems in children: a longitudinal study. Behav Genet. 2011;41:155-164.
14. Rietveld MJH, Hudziak JJ, Bartels M, van Beijsterveldt CEM, Boomsma DI. Heritability of attention problems in children: longitudinal results from a study of twins, age 3 to12. J Child Psychol Psychiatry. 2004;45:577-588.
15. Hudziak JJ, Derks EM, Althoff RR, Rettew DC, Boomsma DI. The genetic and environmental contributions to attention deficit hyperactivity disorder as measured by the Conners' Rating Scales—Revised. Am J Psychiatry. 2005;162:1614-1620.
16. Polderman TJ, Derks EM, Hudziak JJ, Verhulst FC, Posthuma D, Boomsma DI. Across the continuum of attention skills: a twin study of the SWAN ADHD rating scale. J Child Psychol Psychiatry. 2007;48:1080-1087.
17. Derks EM, Hudziak JJ, van Beijsterveldt CEM, Dolan CV, Boomsma DI. A study of genetic and environmental influences on maternal and paternal CBCL syndrome scores in a large sample of 3-year-old Dutch twins. Behav Genet. 2004;34:571-583.
18. Polderman TJ, Posthuma D, De Sonneville LM, Verhulst FC, Boomsma DI. Genetic analyses of teacher ratings of problem behavior in 5-year-old twins. Twin Res Hum Genet. 2006;9:122-130.
19. Derks EM, Hudziak JJ, Van Beijsterveldt CEM, Dolan CV, Boomsma DI. Genetic analyses of maternal and teacher ratings on attention problems in 7-year-old Dutch twins. Behav Genet. 2006;36:833-844.
20. Derks EM, Hudziak JJ, Boomsma DI. Why more boys than girls with ADHD receive treatment: a study of Dutch twins. Twin Res Hum Genet. 2007;10:765-770.
21. van 't Ent D, Lehn H, Derks EM, *et al*. A structural MRI study in monozygotic twins concordant or discordant for attention/hyperactivity problems: evidence for genetic and environmental heterogeneity in the developing brain. Neuroimage. 2007;35:1004-1020.
22. Boomsma DI, Saviouk V, Hottenga J-J, *et al*. Genetic epidemiology of attention deficit hyperactivity disorder (ADHD Index) in adults. PLoS One. 2010;5:e10621.
23. Groen-Blokhuis MM, Middeldorp CM, van Beijsterveldt CEM, Boomsma DI. Evidence for a causal association of low birth weight and attention problems. J Am Acad Child Adolesc Psychiatry. 2011;50:1247-1254.
24. Lehn H, Derks EM, Hudziak JJ, Heutink P, van Beijsterveldt CEM, Boomsma DI. Attention problems and attention-deficit/hyperactivity disorder in discordant and concordant monozygotic twins: evidence of environmental mediators. J Am Acad Child Adolesc Psychiatry. 2007;46:83-91.
25. van 't Ent D, van Beijsterveldt CEM, Derks EM, *et al*. Neuroimaging of response interference in twins concordant or discordant for inattention and hyperactivity symptoms. Neuroscience. 2009; 164:16-29.

26. Robbers SC, van Oort FV, Polderman TJ, *et al*. Trajectories of CBCL attention problems in childhood. Eur J Child Adolesc Psychiatry. 2011;20:419-427.
27. Ehli EA, Abdellaoui A, Hu Y, *et al*. De novo and inherited CNVs in MZ twin pairs selected for discordance and concordance on attention problems. Eur J Hum Genet. 2012;20:1037-1043.
28. Polderman TJ, de Geus EJ, Hoekstra RA, *et al*. Attention problems, inhibitory control, and intelligence index overlapping genetic factors: a study in 9-, 12-, and 18-year-old twins. Neuropsychology. 2009;23:381-391.
29. Polderman TJ, van Dongen J, Boomsma DI. The relation between ADHD symptoms and fine motor control: a genetic study. Child Neuropsychol. 2011;17:138-150.
30. van den Berg SM, Willemsen AHM, de Geus EJ, Boomsma DI. Genetic etiology of stability of attention problems in young adulthood. Am J Med Genet. 2006;141B:55-60.
31. Saviouk V, Hottenga J-J, Slagboom EP, *et al*. ADHD in Dutch adults: heritability and linkage study. Am J Med Genet. 2011;156B:352-362.
32. Distel MA, Carlier A, Middeldorp CM, Derom CA, Lubke GH, Boomsma DI. Borderline personality traits and adult attention-deficit hyperactivity disorder symptoms: a genetic analysis of comorbidity. Am J Med Genet. 2011;156B:817-825.
33. Rietveld MJH, Posthuma D, Dolan CV, Boomsma DI. ADHD: sibling interaction or dominance: an evaluation. Behav Genet. 2003;33:247-255.
34. Boomsma DI, Vink JM, van Beijsterveldt CEM, *et al*. Netherlands Twin Register: a focus on longitudinal research. Twin Res Hum Genet. 2002;5:401-406.
35. Derks EM, Hudziak JJ, Boomsma DI. Genetics of ADHD, hyperactivity, and attention problems. In: Kim Y-K, editor. Handbook of Behavior Genetics. New York: Springer; 2009: p. 361-378.
36. Achenbach TM, Dumenci L, Rescorla LA. DSM-oriented and empirically based approaches to constructing scales from the same item pools. J Clin Child Adolesc Psychol. 2003;32:328–340.
37. Plomin R, DeFries JC, McClearn GE, McGuffin P. Behavioral Genetics. New York.Worth; 2008.
38. Faraone SV, Perlis RH, Doyle AE, *et al*. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57:1313-1323.
39. Burt SA. Rethinking environmental contributions to child and adolescent psychopathology: a meta-analysis of shared environmental influences. Psychol Bull. 2009;135:608-637.
40. Falconer DS, Mackay TFC. Introduction to Quantitative Genetics. Harlow, UK: Addison Wesley Longman; 1996.
41. Gillespie NA, Martin NG. Multivariate Genetic Analysis. In: Everitt BS, Howell DC, eds. Encyclopedia of Statistics in Behavioral Science. Chichester, UK: John Wiley & Sons, Ltd; 2005:1363-1370.
42. Neale MC, Cardon LR. Methodology for Genetic Studies of Twins and Families. Dordrecht, Netherlands: Kluwer Academic; 1992.
43. Kuntsi J, Rijsdijk F, Ronald A, Asherson P, Plomin R. Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. Biol Psychiatry. 2005;57:647-654.
44. Larsson H, Lichtenstein P, Larsson J-O. Genetic contributions to the development of ADHD subtypes from childhood to adolescence. J Am Acad Child Adolesc Psychiatry. 2006;45:973-981.
45. Greven C, Asherson P, Rijsdijk F, Plomin R. A longitudinal twin study on the association between inattentive and hyperactive-impulsive ADHD symptoms. J Abnorm Child Psychol. 2011; 39:623-632.
46. Lamb D, Middeldorp CM, van Beijsterveldt CEM, Boomsma DI. Gene-environment interaction in teacher rated internalizing and externalizing problem behaviour in 7 to 12 year old twins. J Child Psychol Psychiatry. 2012;53:818-825.
47. Owens J, Goldfine M, Evangelista N, Hoza B, Kaiser N. A critical review of self-perceptions and the positive illusory bias in children with ADHD. Clin Child Fam Psychol Rev. 2007;10:335-351.