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LONGITUDINAL MODELING SUGGESTS THAT ADHD SYMPTOMS LEAD TO LOWER EDUCATIONAL ACHIEVEMENT IN CHILDREN

Based on Eveline L. de Zeeuw, Catharina E.M. van Beijsterveldt, Eco J. C. de Geus and Dorret I. Boomsma. (2015). Longitudinal genetic causal modeling suggests that ADHD symptoms lead to lower educational achievement in children. In Preparation.

During childhood there is a negative correlation between Oppositional Defiant Disorder (ODD) and educational achievement and between Attention Deficit Hyperactivity Disorder (ADHD) and educational achievement. Twin studies suggest that the genetic factors influencing ODD/ADHD and educational achievement are also correlated. A genetic correlation can reflect pleiotropy, or can be induced by a causal effect of ODD and ADHD symptoms on educational achievement. In this study, the hypothesis of a causal effect is tested against the hypothesis of genetic pleiotropy using a genetically sensitive design. Complete data on ODD and ADHD symptoms and on educational achievement were available in a cross-sectional sample of 8789 children and in a longitudinal sample of 4540 children, registered with the Netherlands Twin Register. In both sexes, more ODD (boys: $r = -.08$; girls: $r = -.09$) and ADHD (boys: $r = -.16$ to $-.39$; girls: $r = -.12$ to $-.41$) symptoms were associated with lower educational achievement. The observed longitudinal associations were of a similar magnitude. Comparing differences between children from genetically identical twin pairs, girls with more ODD symptoms had lower educational achievement than their co-twin, but this difference was not seen in boys. The twin with more ADHD symptoms scored significantly lower on educational achievement than the co-twin. All genetic correlations between ODD symptoms and educational achievement were significantly different from zero (boys: $r = -.09$ to $-.11$; girls: $r = -.09$ to $-.17$) while most environmental correlations were not. In contrast, for ADHD symptoms and educational achievement, all genetic correlations (boys: $r = -.20$ to $-.48$; girls: $r = -.13$ to $-.48$) and most environmental correlations (boys: $r = -.05$ to $-.33$; girls: $r = -.05$ to $-.37$) were significant. ADHD symptoms may causally lower educational achievement whereas genetic pleiotropic effects are the most likely cause for the association between ODD symptoms low educational achievement.

INTRODUCTION

Low educational achievement in children is an important predictor of continued low achievement and school dropout (Moilanen, Shaw & Maxwell, 2010). The American Psychiatric Association (APA) estimates that 3 to 7 per cent of all school aged children are diagnosed with ADHD and that the prevalence of ODD in children is between 2 to 16 per cent (American Psychiatric Association, 2000). More than 50 per cent of the children diagnosed with ADHD also have ODD (Angold, Costello & Erkanli, 1999). It is well recognized that ODD and ADHD diagnoses can be considered the extreme end of the normal distribution of symptoms in the population (Hudziak et al., 2005; Lubke et al., 2009). In both clinical and population samples, there is a significant negative association between ADHD symptoms and educational achievement (Polderman,

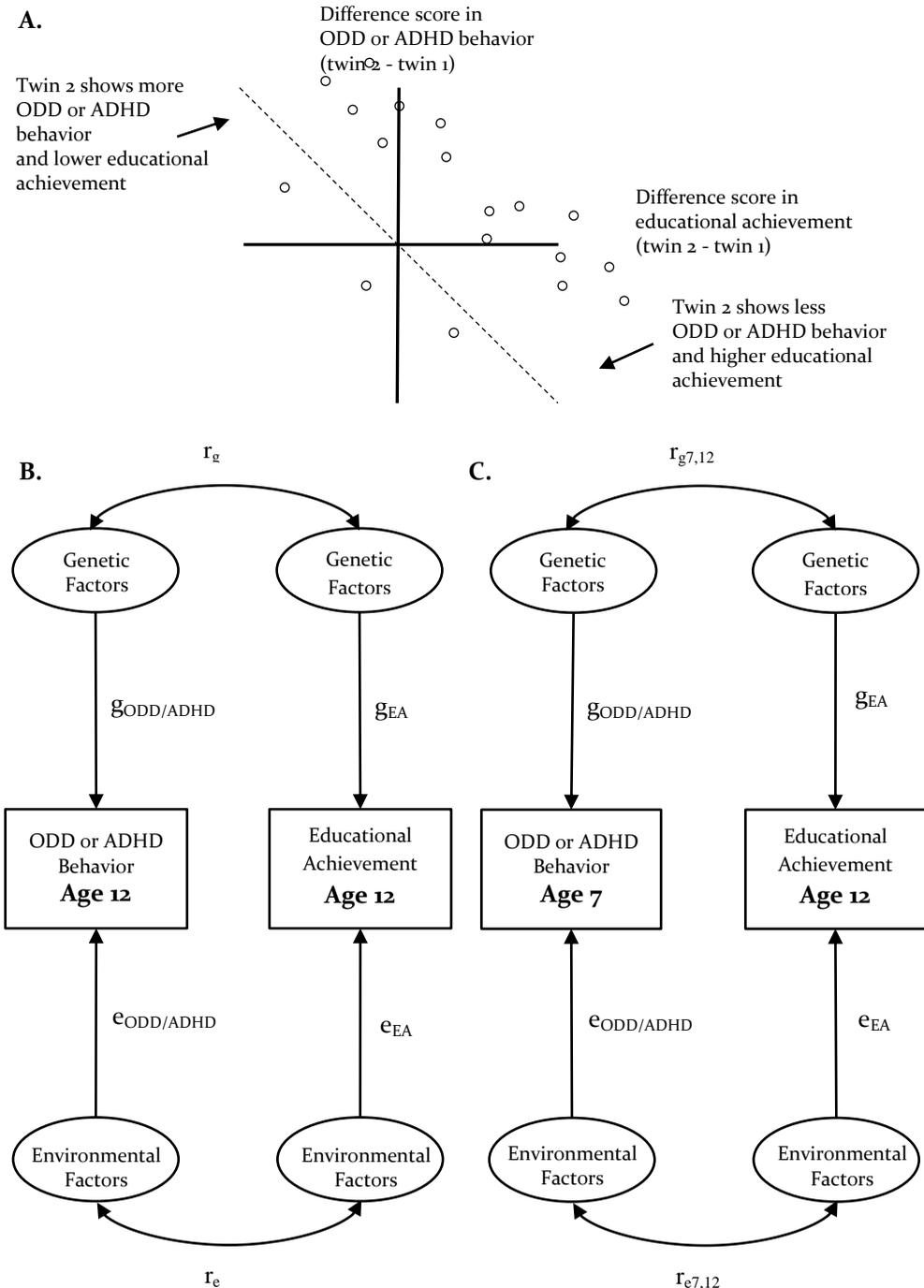
Boomsma, Bartels, Verhulst & Huizink, 2010). Few studies have looked at the association between ODD and educational achievement.

Behavioral genetic studies have established that ADHD is amongst the most heritable psychiatric childhood disorders. According to a review of 20 twin studies, the mean estimate of the heritability of ADHD in children is over 75 per cent (Faraone et al., 2005). Estimates for ODD are somewhat lower with a heritability of around 50 per cent (Hudziak et al., 2005). Educational achievement shows a relatively consistent etiology with a moderate to high influence of genes and a small influence of common environmental factors (Bartels et al., 2002; Haworth et al., 2011). Twin studies have already shown that the (longitudinal) association between ADHD symptoms and educational achievement can to a large extent be attributed to an overlap in genetic factors (Greven et al., 2014; Kuntsi et al., 2004; Saudino & Plomin, 2007). Recently, the genetic correlation between ADHD symptoms and educational achievement has also been demonstrated by a significant prediction of ADHD symptoms in children by polygenic scores which were based on the effect sizes of genetic variants, measured at the genotype level, from a genome-wide association study towards educational attainment in adults (de Zeeuw et al., 2014). The other way around, polygenic scores on genetic variants associated with clinical ADHD predicted general cognitive ability in the general population (Martin et al., 2014). There are two explanations for the observed genetic correlation between ODD and ADHD symptoms and educational achievement. One explanation is genetic pleiotropy, which is when the same genes through the same underlying biological mechanisms, for example brain processes, affect ODD or ADHD symptoms as well as educational achievement. Another possible explanation for the observed genetic correlation is that there is a causal effect of ODD or ADHD on educational achievement which makes it harder to concentrate at school, eventually leading to lower educational achievement. The genetic variants influencing ODD or ADHD would then, through the causal chain, also influence educational achievement.

In the present study we test, in a large population sample, the hypothesis of a causal effect of ODD and ADHD symptoms on educational achievement against the alternative hypothesis of genetic pleiotropy. There are several testable predictions that follow from the causal hypothesis (de Moor et al, 2008). A first prediction is that within pair differences in ODD and ADHD symptoms should be associated with within pair differences in educational achievement in genetically identical or monozygotic (MZ) twins as it excludes confounding by genes and shared environment by the twins such as childhood neighborhood and parental SES. A child, from a MZ twin pair, who shows more ODD or ADHD symptoms than his or her co-twin should also perform worse in school. A non-

significant correlation would point to genetic factors driving the association between ODD or ADHD symptoms and educational achievement while a significant correlation would support the causal hypothesis (Figure 1A). A second prediction is that if ODD or ADHD symptoms have a causal effect on educational achievement, all factors with an effect on ODD or ADHD symptoms should also have an effect on educational achievement. This also holds for the latent genetic and environmental factors detected in a twin study. The correlation between the latent genetic and environmental factors influencing the two phenotypes can be tested in a cross-sectional correlational twin model (Neale, Røysamb & Jacobson, 2006) (Figure 1B). A third, related, prediction is that the association between ODD or ADHD symptoms and educational achievement also exists longitudinally and that the same genetic and environmental factors influencing ODD or ADHD at baseline also influence educational attainment at follow-up. This can be tested in a longitudinal correlational twin model (Neale, Røysamb & Jacobson, 2006) by computing the genetic and environmental correlations over time (Figure 1C). The finding that the genetic correlations as well as the environmental correlations are significant in the cross-sectional and longitudinal models would be in support of, not evidence for, the causal hypothesis. If only the genetic correlations are significant, the causal hypothesis would be rejected, and genetic pleiotropy would be more likely.

FIGURE 1 Graphic representation of the three models, MZ within twin pair differences model (A), cross-sectional correlational model (B) and longitudinal correlational model (C), used to test the causal effect of ODD and ADHD symptoms on educational achievement



METHODS

PARTICIPANTS

The Netherlands Twin Register (NTR), established around 1987 by the department of Biological Psychology at the VU University Amsterdam, registers approximately 40 per cent of all multiple births in the Netherlands. The parents of the twins receive a survey about the development of their children every two years until the twins are 12 years old (Bartels et al., 2007; van Beijsterveldt et al., 2013). The survey sent to the parents includes, amongst others, the short version of the Conners' Parent Ratings Scale - Revised (CPRS-R). In addition, when the children are approximately 12 years old, parents are asked to report the scores of their children on a national test of educational achievement, which is administered in the final grade of primary school (Cito, 2002).

Data on ODD and/or ADHD symptoms are available for age 7 and age 12 while data on educational achievement are only available for age 12. 8789 children had data on ODD and/or ADHD symptoms at age 12 as well as data on educational achievement at age 12. 4406 children only had data on ODD and/or ADHD symptoms at age 12 and 1555 children only had data on educational achievement at age 12 (cross-sectional sample). 4540 children had data on ODD and/or ADHD symptoms at age 7 as well as data on educational achievement at age 12. 8594 children only had data on ODD and/or ADHD symptoms at age 7 and 5804 children only had data on educational achievement at age 12 (longitudinal sample). Children with a disease or handicap that interfered severely with daily functioning were excluded for this study. The cross-sectional sample included 2479 twin pairs of opposite sex. For the same-sex twin pairs, determination of zygosity status was based on blood or DNA polymorphisms ($N=1124$) or on the basis of parental report of items on resemblance in appearance and confusion of the twins by parents and others ($N=3950$). The longitudinal sample included 3169 twin pairs of opposite sex. For the same-sex twin pairs, determination of zygosity status was based on blood or DNA polymorphisms ($N=1072$) or on the basis of the earlier described parental report ($N=5510$). The parental report establishes zygosity with an accuracy of approximately 93 per cent (Rietveld et al., 2000).

MEASUREMENTS

A national standardized test of educational achievement is administered in the final grade of primary school at approximately 80 per cent of all schools in the Netherlands. This test measures what a child has learned across all grades of primary school and is used to give a recommendation about the level of secondary education suitable for the child. The test consists of multiple choice items in four different domains, namely Arithmetic, Language, Study Skills and

Science and Social Studies. The first three test scales are combined into a Total Score, standardized on a scale from 500 and 550, which is used in this study to measure educational achievement.

ODD and ADHD symptoms were assessed, by mothers, with the short version of the Conners' Parent Rating Scales - Revised (CPRS-R). The CPRS-R consists of 27 items scored on a 4 point scale from 0 (not true or never) to 3 (completely true or very often). The CTRS-P includes 4 scales measuring Oppositional Behavior (OPP: 6 items), Inattention (ATT: 6 items), Hyperactivity (HYP: 6 items) and Attention Deficit Hyperactivity Disorder Index (ADHD: 12 items). Three items are included in both the ATT and ADHD scale ('Avoids, or has difficulties in engaging in tasks for a longer period of time', 'Has trouble concentrating in class' and 'Does not follow instructions or finish homework'). Sum scores for the number of symptoms were computed when subjects had no or a limited number of missing items on a scale. Missing items were imputed by the rounded averaged item score of the scale for that child. Sum scores showed an L-shaped distribution and therefore the data were square root transformed prior to analyses.

STATISTICAL ANALYSES

The causal effect of ODD and ADHD symptoms on educational achievement was tested in three different models (de Moor et al, 2008).. The first two testable hypotheses were based on cross-sectional data, the MZ twin within pair differences model and the cross-sectional correlational model, while the third one, the longitudinal correlational model, was based on longitudinal data.

For the first hypothesis, the difference in ODD or ADHD symptoms and the difference in educational achievement between twins from MZ twin pairs were computed and correlated within the twin pairs in SPSS 21.0 (IBM Corp, 2012). The use of data from MZ twin pairs removes possible confounding by genes and shared environment since the MZ twin pairs are genetically identical and grow up in partly the same environment. A significant correlation between ODD or ADHD symptoms and educational achievement would indicate that the association is not merely due to genes or shared environment and would support a causal hypothesis, whereas a non-significant correlation would support genetic pleiotropy.

For the second and third hypothesis, it was assessed whether the cross-sectional association between ODD or ADHD symptoms at age 12 and educational achievement at age 12 and the longitudinal association between ODD or ADHD at age 7 and educational achievement at age 12 were paralleled by significant genetic and environmental correlations.

Cross-sectional and longitudinal models were fitted to the data in the R (R Core Team, 2014) package OpenMx Version 3.1.0 (Boker S.M. et al., 2011; Boker et al., 2012) using raw data maximum likelihood estimation. The analyses were run separately for each scale of the CPRS-R. A model that freely estimated all parameters, i.e. means, variances and covariances, separately for the different zygosity-by-gender groups (MZm, DZm, MZf, DZf and DOS), was fitted to the data (saturated model).

The difference in resemblance between monozygotic (MZ), sharing (nearly) all genes, and dizygotic (DZ) twin pairs, sharing approximately 50 per cent of their segregating genes, was used to estimate the contribution of genes (heritability) and the environment to the different phenotypes. Similarly to the decomposition of variance in a univariate model (Plomin et al., 2008), the cross-twin and cross-phenotype correlation between MZ and DZ twin pairs forms the basis to estimate the genetic and the environmental correlations between phenotypes.

Genetic and environmental correlations were estimated in a series of bivariate genetic models, which included three latent factors, i.e. additive genetic factors (A), common environmental (C) and unique (E) environmental factors (Neale, Røysamb & Jacobson, 2006). Estimates for the influence of the latent factors on ODD symptoms, ADHD symptoms and educational achievement, were estimated separately for boys and girls. Means were allowed to be different between boys and girls for all phenotypes. A causal effect of ODD and ADHD symptoms on educational achievement implies that all genetic and environmental factors influencing ODD and ADHD symptoms affect educational achievement. This implies that both genetic and environmental correlations should be significant.

Significance testing was done by constraining parameter values at zero and comparing the fit of the submodel to that of the unconstrained model. Testing the significance of the correlation between the common environmental factors is only possible when individual differences in both ODD or ADHD symptoms and educational achievement are influenced by the common environment. If there is no variation in ODD or ADHD symptoms accounted for by common environmental factors there will be no common environmental correlation between ODD or ADHD symptoms and educational achievement. In this case, the causal hypothesis will be supported when both the genetic and unique environmental correlation are significant. The difference in goodness of fit between nested models was assessed by log-likelihood ratio tests (LRT) which calculate the difference in $-2\log$ -likelihood ($-2LL$) between two models and evaluates this χ^2 -statistic with the difference in the number of estimated

parameters between the models as degrees of freedom. A p-value smaller than 0.05 was considered significant.

RESULTS

Table 1 presents the means and standard deviations for boys and girls, for ODD and ADHD symptoms at age 7 and 12 and educational achievement at age 12. The cross-sectional and longitudinal phenotypic correlations between ODD or ADHD symptoms and educational achievement are given in Table 2. These correlations tend to be small for ODD symptoms, but all estimates were significant. The cross-sectional and longitudinal phenotypic correlations between ADHD symptoms and educational achievement are larger, and also more variable, depending on the subtype of symptoms. The longitudinal phenotypic correlations are rather similar to the cross-sectional phenotypic correlations.

TABLE 1 Means and standard deviations (SD) for ODD and ADHD symptoms and educational achievement

	Boys			Girls		
	N	Mean	SD	N	Mean	SD
Oppositional Behavior						
Age 7	6559	4.27	3.51	6530	3.61	3.16
Age 12	6487	3.75	3.31	6685	3.30	3.03
Inattention						
Age 7	6524	3.66	4.11	6484	2.44	3.31
Age 12	6484	3.75	4.09	6682	2.32	3.08
Hyperactivity						
Age 7	6562	3.41	3.63	6533	2.03	2.65
Age 12	6488	2.01	2.80	6687	1.06	1.89
ADHD Index						
Age 7	6555	8.47	7.65	6521	5.90	6.17
Age 12	6489	7.67	7.25	6681	4.96	5.59
Educational Achievement						
Age 12	4950	538.5	8.3	5394	537.1	8.7

The correlations for within MZ pair differences in ODD or ADHD symptoms and educational achievement are also reported in Table 2. The correlation was significant for ODD symptoms and educational achievement in girls but not in boys. Girls from MZ pairs with more ODD symptoms perform less in school than their sisters. For boys this is not seen. The correlations between the MZ twin pair differences for ADHD symptoms and educational achievement were significant for both boys and girls. Thus, in genetically identical twin pairs, the twin with more ADHD symptoms has a lower educational achievement than his or her co-twin. As within these twin pairs there is no confounding by genes, the within-pair association between ODD symptoms, and even more so, ADHD symptoms and educational achievement cannot reflect genetic pleiotropy. They therefore more likely reflect causality.

TABLE 2 Monozygotic within twin pair differences correlations, cross-sectional correlations and longitudinal correlations (N) for ODD and ADHD symptoms with educational achievement

	Oppositional Behavior	Inattention	Hyperactivity	ADHD Index
Cross-sectional Correlation				
Boys	-.08* (4218)	-.39** (4214)	-.16** (4216)	-.32** (4218)
Girls	-.09* (4560)	-.41** (4558)	-.12** (4561)	-.33** (4566)
Longitudinal Correlation				
Boys	-.09** (2149)	-.32** (2143)	-.16** (2155)	-.27** (2146)
Girls	-.11** (2376)	-.33** (2359)	-.17** (2374)	-.28** (2368)
MZ Differences Correlation				
Boys	-.04 (678)	-.29** (686)	-.10* (687)	-.31** (687)
Girls	-.11* (834)	-.34** (835)	-.11* (838)	-.31** (836)

* $p < .01$; ** $p < .001$

The twin correlations as estimated in the cross-sectional and longitudinal correlational models are summarized in Table 3 and 4. All MZ within phenotype correlations were larger than the DZ correlations. Most MZ cross-correlations between ODD symptoms and educational achievement and between ADHD symptoms and educational achievement were significant and higher than the DZ cross-correlations. This pattern of correlations suggests that there is a genetic correlation which is at least partly responsible for the cross-sectional

and longitudinal associations between ODD and ADHD symptoms and educational achievement.

TABLE 3 Cross-sectional cross-twin within-phenotype (upper) and cross-twin cross-phenotype (lower) correlations (95% Confidence Interval) for ODD and ADHD symptoms at age 12 and educational achievement at age 12

	Educational Achievement	Oppositional Behavior	Inattention	Hyperactivity	ADHD Index
MZm	.81 (.78; .83)	.73 (.70; .76)	.74 (.72; .77)	.82 (.80; .84)	.77 (.74; .79)
DZm	.46 (.39; .51)	.43 (.38; .48)	.29 (.24; .35)	.39 (.34; .43)	.34 (.29; .39)
MZf	.83 (.81; .85)	.70 (.67; .73)	.74 (.71; .76)	.80 (.78; .82)	.76 (.73; .78)
DZf	.43 (.37; .48)	.46 (.41; .50)	.27 (.21; .33)	.42 (.37; .47)	.29 (.23; .34)
DOS	.44 (.40; .48)	.41 (.37; .45)	.27 (.23; .31)	.38 (.35; .42)	.29 (.25; .33)
MZm		-.16 (-.24; -.07)	-.31 (-.39; -.23)	-.17 (-.26; -.08)	-.27 (-.35; -.18)
DZm		-.06 (-.14; .02)	-.06 (-.13; .02)	-.04 (-.12; .04)	-.08 (-.15; .00)
MZf		-.11 (-.19; -.02)	-.22 (-.30; -.13)	-.05 (-.14; .03)	-.19 (-.27; -.10)
DZf		-.05 (-.13; .03)	-.06 (-.13; .02)	-.09 (-.17; -.01)	-.04 (-.12; .04)
DOS		-.07 (-.13; -.02)	-.13 (-.18; -.08)	-.14 (-.20; -.09)	-.12 (-.17; -.06)

MZm = monozygotic boys; DZm = dizygotic boys; MZf = monozygotic girls; DZf = dizygotic girls; DOS = dizygotic of opposite-sex

Table 5 includes the estimates and 95% confidence intervals of the cross-sectional genetic and environmental correlations between ODD or ADHD symptoms at age 12 and educational achievement at age 12. The genetic correlations between ODD symptoms and educational achievement were significant as was the environmental correlation in girls, but the environmental correlation in boys was not significantly different from zero. The genetic correlations and environmental correlations between ADHD symptoms and educational achievement were all significant. This applied to both the ATT and HYP subscales.

TABLE 4 Longitudinal cross-twin within-phenotype (upper) and cross-twin cross-phenotype (lower) correlations (95% Confidence Interval) for ODD and ADHD symptoms at age 7 and educational achievement at age 12

	Educational Achievement	Oppositional Behavior	Inattention	Hyperactivity	ADHD Index
MZm	.81 (.78; .83)	.72 (.69; .74)	.77 (.75; .80)	.78 (.75; .80)	.82 (.80; .84)
DZm	.46 (.39; .51)	.41 (.35; .46)	.23 (.18; .29)	.29 (.23; .34)	.28 (.23; .34)
MZf	.83 (.81; .85)	.74 (.71; .76)	.70 (.67; .72)	.75 (.73; .78)	.75 (.72; .77)
DZf	.43 (.37; .48)	.44 (.38; .48)	.24 (.18; .30)	.35 (.29; .40)	.33 (.27; .38)
DOS	.44 (.40; .48)	.41 (.38; .45)	.19 (.15; .23)	.29 (.25; .33)	.29 (.25; .32)
MZm		-.10 (-.16; -.03)	-.37 (-.42; -.31)	-.14 (-.21; -.08)	-.29 (-.35; -.23)
DZm		-.05 (-.11; .00)	-.07 (-.12; -.01)	-.06 (-.11; -.00)	-.06 (-.12; -.00)
MZf		-.07 (-.13; -.01)	-.32 (-.37; -.27)	-.07 (-.13; -.00)	-.26 (-.31; -.20)
DZf		-.06 (-.12; .00)	-.03 (-.09; .03)	-.02 (-.08; .04)	-.03 (-.09; .03)
DOS		-.06 (-.10; -.02)	-.11 (-.15; -.08)	-.09 (-.13; -.05)	-.09 (-.13; -.06)

MZm = monozygotic boys; DZm = dizygotic boys; MZf = monozygotic girls; DZf = dizygotic girls; DOS = dizygotic of opposite-sex

TABLE 5 Cross-sectional genetic and environmental correlations (95% Confidence Interval), separately for boys and girls, for ODD and ADHD symptoms at age 12 with educational achievement at age 12

	Oppositional Behavior	Inattention	Hyperactivity	ADHD Index
Genetic Correlation				
Boys	-.09 (-.15; -.04)	-.48 (-.54; -.42)	-.20 (-.25; -.15)	-.37 (-.42; -.32)
Girls	-.09 (-.14; -.04)	-.48 (-.53; -.43)	-.13 (-.18; -.08)	-.37 (-.42; -.33)
Environmental Correlation				
Boys	-.02 (-.10; .06)	-.30 (-.37; -.23)	-.10 (-.17; -.02)	-.33 (-.39; -.26)
Girls	-.09 (-.16; -.02)	-.37 (-.43; -.31)	-.11 (-.18; -.04)	-.34 (-.40; -.28)

Table 6 gives the estimates and 95% confidence intervals of the longitudinal genetic and environmental correlations between ODD and ADHD symptoms at age 7 and educational achievement at age 12. The genetic correlations were significant for ODD symptoms but the environmental correlations were not.

The genetic correlations between the different subtypes of ADHD symptoms and educational achievement were all significant whereas the environmental correlations were significant for ATT and ADHD but not HYP. Taken together, table 5 and 6 show that all latent factors influencing ADHD symptoms also influenced current and future educational achievement, in keeping with the predictions from the causal hypothesis.

TABLE 6 Longitudinal genetic and environmental correlations (95% Confidence Interval), separately for boys and girls, for ODD and ADHD symptoms at age 7 with educational achievement at age 12

	Oppositional Behavior	Inattention	Hyperactivity	ADHD Index
Genetic Correlation				
Boys	-.11 (-.18; -.03)	-.40 (-.47; -.33)	-.21 (-.27; -.14)	-.32 (-.39; -.25)
Girls	-.17 (-.25; -.09)	-.39 (-.45; -.33)	-.19 (-.25; -.13)	-.35 (-.41; -.29)
Environmental Correlation				
Boys	-.01 (-.11; .08)	-.16 (-.26; -.05)	-.05 (-.14; .05)	-.19 (-.28; -.09)
Girls	.01 (-.09; .11)	-.17 (-.27; -.07)	-.05 (-.15; .05)	-.13 (-.23; -.03)

DISCUSSION

The aim of the present study was to determine whether the observed genetic correlation between ODD and ADHD symptoms and educational achievement is best explained by a causal effect of ODD or ADHD symptoms on educational achievement, or by genetic pleiotropy. In line with earlier research we found significant negative associations between ODD and ADHD symptoms and educational achievement (Polderman et al., 2010)(Polderman et al., 2010). Children, who displayed more ODD or ADHD symptoms, as rated by their mother at the same time or 5 years earlier, scored lower on a standardized educational achievement test. Comparing the different components of ADHD, inattentiveness and hyperactivity, suggests variation in the magnitude of the association with educational achievement. Inattentiveness is to a much greater extent related to educational achievement than hyperactivity.

For ODD symptoms the association within genetically identical twin pairs was rather small and only significant for girls and not boys. Moreover, the cross-sectional and longitudinal genetic correlations between ODD symptoms and

educational achievement were significant, but most environmental correlations were not. Absence of significant environmental correlations implies that a causal effect of ODD symptoms on educational achievement is falsified and that genetic pleiotropy underlies the association. However, power to detect an environmental correlation was low, a large number of complete twin pairs are necessary when the phenotypic correlation is small, which is the case for the association between ODD symptoms and educational achievement (boys: $r = -.08$; girls: $r = -.09$) (de Moor et al, 2008).

Within genetically identical twin pairs, the twin who showed more ADHD symptoms scored lower on the educational achievement test than his or her co-twin. Thus, even when correcting for possible confounding by genes, the association remained significant. The cross-sectional and longitudinal genetic correlations between ADHD symptoms and educational achievement were significant, as were the environmental correlations. This supports the causal effect of ADHD symptoms on educational achievement.

Taken together, the tests do not support a causal effect of ODD symptoms on educational achievement. However, this rejection of the causal hypothesis should be treated with caution as there was a lack of power to detect an environmental correlation due to the small phenotypic correlation that is observed between ODD symptoms and educational achievement (de Moor et al, 2008).

The tests fully supported the causal effect of ADHD symptoms on educational achievement. This indicates that a behavioral intervention or medication prescription, leading to a reduction in symptoms of ADHD (King et al., 2006; Schachter et al., 2001), will also indirectly, through the causal chain, improve the educational achievement of children. The effects of prescription of medication for ADHD on the performance at school have been investigated in earlier research. When medication use resulted in a decrease in symptoms of ADHD, children were indeed better able to stay focused and completed more of their school work (Brown et al., 2005; Prasad et al., 2013). The influence on the actual educational achievement was only modest and evidence was less convincing.

A limitation of this study is that it could not test the direction of the causality and more complex mechanisms of causality, such as bidirectional causality, or a combination of pleiotropy and a reverse causal effect of low educational achievement on ODD and ADHD symptoms. Children who have problems keeping up in school display, perhaps out of frustration, ODD or ADHD symptoms. Bidirectional causality implies that ODD or ADHD symptoms lead to lower educational achievement and in turn problems at school enhance the already existing symptoms. There are direction of causality models that could be

used to study these more complex mechanisms (Duffy & Martin, 1994; Heath et al., 1993). However, to be able to resolve the direction of the causal association these models require a substantial difference in heritability, which is not the case for either ODD or ADHD symptoms and educational achievement.

ODD and ADHD symptoms were found to be associated, both cross-sectional and longitudinal, with lower educational achievement in primary school children. The results for ODD symptoms and educational achievement were somewhat inconsistent, probably due to a lack of power, and the causal hypothesis could not be supported. The results for ADHD symptoms and educational achievement were in line with a causal effect of ADHD symptoms on educational achievement. A practical implication following from the causal effect of ADHD symptoms on educational achievement is that, when a behavioral intervention or medication prescription leads to a reduction in ADHD symptoms, it could also have an enhancing influence on educational achievement. This effect will probably be larger for children displaying inattentive symptoms compared to children mainly demonstrating hyperactive symptoms given the difference in the strength of the association with educational achievement.

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