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This is a Peer Reviewed Accepted version of the following article, accepted for publication in American Journal of Medical Genetics Part B: Neuropsychiatric Genetics.

2017-07-07

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Am J Med Genet B Neuropsychiatr Genet. 2017 Jul;174(5):538-546.

<http://doi.org/10.1002/ajmg.b.32536>

<http://hdl.handle.net/10616/45980>

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Genetic and environmental contributions to the association between ADHD and affective problems in early childhood – a Swedish population-based twin study

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Running head: ADHD and affective problems in preschool twins

Total word count: 4766

Abstract word count: 250

Number of figures/tables: 6

Supplementary Tables: 3

ABSTRACT

Few twin studies have explored the relative contribution of genetic and environmental factors to the association between attention deficit hyperactivity disorder (ADHD) and affective problems, and no study has focused on preschool children. We used the classical twin design to explore the genetic and environmental overlap between ADHD symptoms and affective problems in preschool children, based on 879 five-year-old twin pairs born in Sweden 2004-2005. Questionnaire-based parent-ratings were used to measure ADHD symptoms and affective problems. A bivariate twin design was used to decompose variance in ADHD and affective problems into genetic and environmental components, and to test the degree to which these components overlapped across the two traits. Our results showed that there was a significant correlation of 0.34 (95% Confidence Interval [CI] 0.29-0.38) between ADHD and affective problems. This correlation was mostly explained by additive genetic factors (64%, 95% CI 37-93%), and to a lesser extent by shared environmental factors (35%, 95% CI 10-59%). Nonshared environmental factors did not contribute to the correlation between ADHD and affective problems (0%, 95% CI -9-10%). These findings show that there is a significant association between ADHD and affective problems in preschool children that is mostly explained by genetic influences. This adds important knowledge about the etiology of both ADHD and affective problems by indicating that these phenotypes are linked from as early as preschool years. This also needs to be taken into consideration when diagnosing young children and clinicians should consider assessing both affective problems and ADHD if one is present.

Key words: ADHD, affective problems, comorbidity, twin study

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of hyperactivity-impulsivity and inattention. ADHD frequently co-occurs with affective disorders, such as anxiety and depression [Angold et al., 1999; McGough et al., 2005; Michielsen et al., 2013]. The co-occurrence of these two disorders has been associated with greater social impairment, poorer academic functioning and more psychiatric problems, as well as with suicide and higher levels of substance use later in life [Biederman et al., 2008; Blackman et al., 2005; Daviss, 2008]. Despite this established co-occurrence of ADHD and affective problems, reasonably little is known about why these disorders co-occur.

Both ADHD and affective disorder have been shown to be heritable in young people [Posthuma and Polderman, 2013; Rice et al., 2002]. It has been suggested that disorders such as these are better defined as the extreme end of a continuous distribution of characteristic traits, rather than as a categorical disorder [Plomin et al., 2009]. ADHD has been shown to be heritable regardless if it is assessed as a categorical disorder or a continuous trait [Larsson et al., 2012; Levy et al., 1997], suggesting a genetic link between clinical ADHD and milder traits of ADHD.

Family studies suggest that relatives of individuals with ADHD are at a heightened risk of developing affective problems, suggesting shared familial influences on these disorders [Biederman et al., 1991; Faraone and Biederman, 1997]. Family studies are limited, however, in that they cannot tell us whether shared genetics or environmental factors are driving the association between ADHD and affective problems. Twin studies show that there is a strong genetic influence on ADHD symptoms, whereas shared environmental influences have been

shown to be of limited, if any, importance [Burt, 2009; Burt et al., 2012], although it has been argued that methodological issues with twin studies might prevent finding a significant effect of shared environmental factors [Wood et al., 2010]. Affective disorders, on the other hand, seem to be influenced by both genetic factors and shared environmental factors, where shared environmental factors seem to be particularly influential among younger children [Rice et al., 2002]. However, few previous twin studies have explored the relative contribution of genetic and environmental factors to the association between ADHD symptoms and affective problems [Chen et al., 2015; Cole et al., 2009; Michelini et al., 2015; Spatola et al., 2007].

Cole et al. (2009) found that shared genetic factors explained most of the association between traits of ADHD and depression. Similar results were found by Spatola et al. (2007), who used a multivariate twin analysis to study the overlap between different subscales of the Child Behavior Check List (CBCL), such as affective problems, anxiety problems, and attention-deficit/hyperactivity problems. Chen et al. (2015), on the other hand, found that both common genetic and shared environmental influences explained the overlap between ADHD traits and three internalizing problem scales. Furthermore, it has previously been shown that although there is an important overlap of genetic influences for the two dimensions of ADHD (inattention and hyperactivity/impulsivity) there is some genetic independence as well [McLoughlin et al., 2007]. Thus, it is possible that the association between ADHD and affective problems differs by ADHD symptom domain. This has rarely been tested; a recent twin study by Michelini et al. found that the association between ADHD traits and anxiety was driven by inattention, rather than hyperactivity/impulsivity [Michelini et al., 2015].

None of these previous twin studies focus on pre-school children, preventing the possibility to detect potential differences in the genetic and environmental underpinnings of the association between traits of ADHD and affective problems during different developmental periods. This

is an important limitation as previous studies indicate that the influence of genetic and shared environmental factors for depression differ during different age periods [Rice et al., 2002], and it has also been shown that young children with ADHD traits score higher on rating scales measuring internalizing behavior [Sinzig et al., 2014]. Given the potential functional impairment and worse prognosis of depression among children with co-occurring ADHD and depression [Daviss, 2008], it is important to assess younger age groups to clarify if ADHD symptoms and affective problems co-occur in early ages. Therefore, the relative contribution of genetic and environmental factors to the overlap between ADHD and affective problems in young children remains to be elucidated.

The aim of this study was thus to explore the genetic and environmental overlap between ADHD symptoms and affective problems in preschool children using the classical twin design.

MATERIALS AND METHODS

Study population

The study was based on the Preschool Twin Study in Sweden (PETSS). The overall aim of PETSS was to investigate how genes and environment in early childhood contribute to the development of behavioral problems. All twins born in Sweden between January 2004 and May 2005 were identified through the Swedish population-based medical birth register. Parents of these twins (1,261 twin pairs) were contacted one month prior to the twins 5th birthday and asked to fill in a questionnaire. Parents were approached separately, resulting in 828 (65%) responses from mothers and 698 (55%) responses from fathers. Mother ratings or father ratings were available for 879 twin pairs (1,758 twins).

Zygosity was determined by fitting a 2-class (i.e., monozygotic [MZ] or dizygotic [DZ]) latent class model [Heath et al., 2003] in Mplus Version 4.1 [Muthén and Muthén, 2006] to standard physical similarity questions [Lichtenstein et al., 2007], separately for mother and father reports. In total, 25 twin pairs were excluded due to contradictions between the mother and father reports (20 twin pairs), or due to low predicted probabilities of class membership (five twin pairs were assigned as MZ or DZ with a probability lower than 0.95), resulting in 854 twin pairs (1,708 twins) with assigned zygosity (292 MZ females; 238 DZ females; 284 MZ males; 246 DZ males; and 648 DZ opposite sex).

The study was approved by an ethics committee at Karolinska Institutet (DNR 2007-1034). Parents gave their informed consent for themselves and their children to participate in the study.

Measures

ADHD symptoms were measured with the DuPaul ADHD Rating Scale IV [DuPaul et al., 1998a], reported separately by the mothers and the fathers. The scale consists of 18 items, covering the DSM-IV criteria for ADHD, with four possible responses corresponding to a score of 0-3: *never or rarely*; *sometimes*, *often*, or *very often*. The scores for these items are added together to form an index, ranging from 0 to 54. The DuPaul ADHD Rating Scale has been validated and shown to have good test-retest reliability (Pearson's r : .85) and internal consistency (Cronbach's alpha: .92) [DuPaul et al., 1998b]. Maternal reports were available for 93% of the twins and paternal reports for 79% of the twins. Mother and father ratings were similar, with mean scores of 10.29 (standard deviation (sd): 7.21) and 11.00 (sd: 7.22) respectively, and a Cronbach's alpha of 0.92 for both mother and father ratings. When both

maternal and paternal reports were available, these were combined by taking the average score. If information was only available for one parent, that report was used. Children with missing values for more than 20% of the items in the ADHD scale were treated as missing for the total ADHD score. Furthermore, two subscales were derived to measure the two dimensions of ADHD: inattention and hyperactivity/impulsivity, based on the 9 DSM-IV symptoms respectively.

Affective problems were measured using the DSM-oriented *affective problems* subscale from the Child Behaviour Check List for Ages 6-18 (CBCL/6-18) [Achenbach et al., 2003], reported separately by the mother and the father. The scale has been shown to have good validity when compared with clinical diagnoses of major depression, with an area under the curve value of 0.83 [Ferdinand, 2008]. All items in the CBCL are in the form of a statement about the child's behaviour during the last six months, with the possible responses: 0 = *not true*, 1 = *somewhat or sometimes true*, and 2 = *very true or often true*. The affective problems subscale consists of 12 items, the scores for which are added together to form an index ranging from 0 to 24. Again, mother and father ratings were similar, with means of 1.46 (sd: 1.85) and 1.51 (sd: 1.94), and Cronbach's alpha of 0.61 and 0.64, respectively. Therefore, the average maternal and paternal score was used when both reports were available, and if information was only available for one parent, that report was used. Children with missing values for more than 20% of the items in the affective problems scale were treated as missing for the total score.

Statistical analyses

Both the ADHD scale and the affective problems scale were log transformed to account for skewness in raw scores (see Table 1 for skewness values). To investigate the relative

importance of genetic and environmental factors, we used the twin method. This method relies on comparing genetically identical MZ twin pairs, who share 100% of their segregating alleles, with DZ twin pairs, who share an average 50% of their segregating alleles. Using this information, the variance in, and covariance between, phenotypes is decomposed into additive genetic influences (A), environmental effects that are shared by twins (C), and environmental effects that make twins differ from another (E) [Neale and Maes, 2004].

An initial examination of the relative contributions of A, C and E was based on twin correlations assessing twin similarity for a trait between twins in a pair. In general, MZ correlations higher than DZ correlations indicate influences from A. DZ correlations higher than half the MZ correlations suggest C. The extent to which MZ correlations are less than 1 suggests E, with E incorporating measurement error. We used cross-twin cross-trait correlations (CTCT), i.e. the correlation between twin 1's score on trait 1 and the cotwin's score on trait 2, for an initial examination of the relative contributions of A, C, and E to the covariance between ADHD and affective problems. Phenotypic correlations, intraclass correlations and CTCTs were estimated from a constrained saturated model.

Cholesky decompositions, presented here as the mathematically-equivalent correlated factors solution [Loehlin, 1996], were fitted to data using the OpenMx package [Boker et al., 2011] of R [R Core Team, 2013]. This model assesses the relative contribution of A, C and E to each trait, as well as estimating a genetic (r_A), shared environmental (r_C), and nonshared environmental (r_E) correlation. These correlations indicate the extent of genetic and environmental overlap between two traits, with estimates ranging from 0 (no overlap) to 1 (total overlap). Mean effects of sex were regressed out before structural equation modeling, in

line with standard behavioral genetic procedure [McGue and Bouchard Jr, 1984], and analyses were performed on standardized residual scores.

Both quantitative and qualitative sex differences were considered in the analysis. Quantitative sex differences arise when the relative importance of genetic and environmental influences differs across males and females, and are indicated when the same-sex twin correlations differ across males and females. Qualitative sex differences refer to the instance where different genetic and environmental factors influence a single trait in males and females. Such differences reduce the opposite-sex DZ twin correlation, and are indicated when the opposite-sex twin correlation is less the average of the male and female DZ correlations. They are modeled by permitting the genetic covariance to be freely estimated for opposite-sex twins in the model, rather than constraining it to equal .5. In this study, we investigated the presence of qualitative sex differences in additive genetic influences; due to limited statistical power we did not consider qualitative sex differences in shared environment. We fitted four different ACE models: (i) including qualitative and quantitative sex differences, (ii) including quantitative sex differences only, (iii) including qualitative sex differences only, and (iv) without any sex differences. We also fitted AE models in the same manner, but they did not fit the data better than the corresponding ACE models (contact the first author for details).

Akaike's Information Criterion (AIC) was used to assess the goodness of fit for the different twin models. A lower AIC value indicates a better fit of the model to the observed data, therefore the best-fitting model was defined as the model with the lowest AIC value.

Based on the best fitting model, we calculated the proportion of the phenotypic overlap between ADHD and affective problems explained by A, C, and E, which were calculated from the variance components for each trait and the etiological correlations between them.

To investigate the association between the two subscales of ADHD and affective problems, we fitted a multivariate correlated factors solution of hyperactivity/impulsivity, inattention, and affective problems.

RESULTS

Descriptive statistics for the ADHD and affective problems scales are shown in Table 1. Boys had a significantly higher ADHD score than girls (11.63 [95% CI: 11.17-12.10] compared to 9.44 [95% CI: 9.01-9.86]; $t_{1644}=6.83$, $p < .001$, $d=.34$), whereas no such difference could be seen for affective problems ($t_{1642}= -0.17$, $p=.87$, $d=-.01$).

The phenotypic correlation between ADHD symptoms and affective problems was 0.34 (95% CI 0.29-0.38). Twin correlations for ADHD and affective problems are shown in Table 2. MZ correlations were higher than DZ correlations for each trait, suggesting that A was important for both traits. For girls, DZ correlations for affective problems were higher than half the MZ correlations, indicating the presence of shared environmental influences, C. There seemed to be a similar indication of C for boys as well, but for ADHD symptoms rather than for affective problems. MZ correlations were lower than 1 for both phenotypes, suggesting E. Assessments of CTCTs were focused on point estimates. CTCTs were higher for MZ than DZ, suggesting that the covariance between these traits was influenced by A. For girls, CTCTs for DZ were higher than half the MZ correlations, suggesting that C was important for the overlap between ADHD symptoms and affective problems. There was no such indication

of C for the covariance among boys. CTCTs for MZ were slightly lower than the phenotypic correlation for girls, but not for boys, indicating some influence of E among girls but not among boys.

Model fit characteristics are summarized in Table 3. An ACE model with quantitative sex differences proved to be the best fit of the data. The standardized A, C and E estimates from the ACE model with quantitative sex differences are shown in Figure 1A, separately for boys and girls. The effect of A explained a substantial part of the variance in ADHD symptoms for both boys ($A=0.61$; 95% CI 0.44-0.75) and girls ($A=0.74$; 95% CI 0.62-0.82). The effect of the E factors was similar in magnitude for boys ($E=0.18$; 95% CI 0.14-0.24) and girls ($E=0.21$; 95% CI 0.16-0.27). The effect of C for ADHD symptoms was low for boys ($C=0.21$; 95% CI 0.07-0.36) and not significant for girls ($C=0.05$; 95% CI 0.00-0.15). The effect of A for affective problems was estimated as 0.58 (95% CI 0.36-0.68) and 0.37 (95% CI 0.14-0.57), for boys and girls respectively. The effect of the E factors was similar in magnitude for boys ($E=0.38$; 95% CI 0.30-0.47) and girls ($E=0.36$; 95% CI 0.29-0.45). The effect of the C component was 0.04 for boys (95% CI 0.00-0.22) and 0.27 for girls (95% CI 0.10-0.47).

The genetic correlations between ADHD symptoms and affective problems was statistically significant for both boys ($r_A=0.48$; 95% CI 0.32-0.73) and girls ($r_A=0.34$; 95% CI 0.11-0.58) (see Figure 1A). The shared environmental correlations (r_C) were 1.00 for both boys and girls, although with wide confidence intervals (-1.00-1.00 and 0.66-1.00 respectively). The non-shared environmental correlations were non-significant for boys ($r_E=-0.12$; 95% CI -0.27-0.04) and girls ($r_E=0.14$; 95% CI -0.01-0.29). Even though the model with quantitative sex differences provided the best fit of data, there were no dramatic differences between boys and girls. Furthermore, since the model without sex differences generates more precise

parameter estimates (i.e., increased statistical power which generates tighter confidence intervals), results are also shown based on the model without any sex differences in Figure 1B.

Figure 2 shows the proportion of the correlation between ADHD symptoms and affective problems explained by A, C and E respectively. Results are presented based on the model without sex differences, even though the model with quantitative sex differences fitted data significantly better, because the weak negative non-shared environmental correlation for boys constrains possibilities to calculate the degree of covariance between ADHD and affective problems explained by E. The overlap between ADHD symptoms and affective problems was largely due to genetic factors; A explained 64% of the phenotypic correlation (95% CI 37-93%), with some contribution of shared environmental influences (proportion explained by C: 35%, 95% CI 10-59%) whereas there was no influence of non-shared environmental factors as the proportion explained by E was 0% (95% CI -9-10%).

Subscale analyses

The phenotypic correlations between ADHD subscales and affective problems were similar for the two ADHD symptom dimensions and across sex. The phenotypic correlation of inattention and affective problems was 0.31 (95% CI 0.24-0.37) for males and 0.29 (95% CI 0.23-0.36) for females. Similarly, the correlations between hyperactivity/impulsivity and affective problems were 0.27 (95% CI 0.20-0.34) and 0.31 (95% CI 0.24-0.37) for males and females respectively. Twin correlations and model fit characteristics are shown in Supplementary Tables 1 and 2. An AE model with quantitative sex differences proved to be the best fit of the data. Standardized A and E estimates from the model are shown separately for boys and girls in Figure 3. The effect of A explained a substantial part of the variance in

all three traits, although with slightly higher estimates for hyperactivity/impulsivity. Likewise, the effect of the E factors was similar in magnitude for all traits. There was genetic overlap between both subscales of ADHD and affective problems, with genetic correlations varying from 0.40 to 0.49. On the other hand, the environmental correlations of the two ADHD symptom dimensions with affective problems were not statistically significant. There were no clear differences between boys and girls regarding variance components, genetic and environmental correlations, or proportion of phenotypic correlations explained by A and E. The phenotypic correlations of the two ADHD dimensions with affective problems were almost completely explained by A, with no significant contribution of E, both for inattention and hyperactivity/impulsivity, and for both boys and girls (see Supplementary Table 3).

DISCUSSION

In this study of preschool twins, we found ADHD symptoms and affective problems to be significantly associated with each another in five-year old children, with a phenotypic correlation similar to what has been reported in previous studies [Chen et al., 2015; Spatola et al., 2007]. There was a substantial degree of genetic overlap between ADHD symptoms and affective problems, which is in line with previous twin studies on the association between ADHD symptoms and affective problems in older age groups [Chen et al., 2015; Cole et al., 2009; Michelini et al., 2015; Spatola et al., 2007].

Our findings extend previous research by showing that the genetic overlap between ADHD symptoms and affective problems is already present in early childhood. These findings have implications for etiology as it has not yet been established why ADHD and affective problems co-occur. Several explanations have been suggested previously, for instance that ADHD might influence the development of affective problems through increased psychosocial

impairment related to ADHD, or that ADHD and affective problems co-occur due to shared familial risk factors – either of genetic or environmental nature [Daviss, 2008; Meinzer et al., 2014]. While we could not address the first hypothesis in this study since it was based on a cross-sectional design, our findings instead support the notion of a shared genetic liability of both ADHD symptoms and affective problems in young children.

Genetic overlap between ADHD and affective disorders has been found in molecular genetic studies. For instance, a recent study using SNPs found a genetic correlation between ADHD and affective problems of similar magnitude as in this study [Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a]. Furthermore, in another publication from the same consortia, the authors identified several genetic risk variants that were associated with several psychiatric disorders, including ADHD and major depressive disorder [Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013b]. Further studies are needed to disentangle the nature of this genetic overlap, for instance by looking at associations between polygenic risk scores of ADHD and affective disorders.

We found a statistically significant effect of shared environmental influences on ADHD symptoms, which is inconsistent with recent meta-analyses [Burt, 2009; Nikolas and Burt, 2010], but consistent with a few previous twin studies [Chen et al., 2015; Larsson et al., 2004; Taylor et al., 2013]. Also, findings from a recent extended family study comparing maternal and paternal half-siblings indicate that a small part of the familial aggregation of ADHD is due to shared environmental influences [Chen et al., 2016]. As Wood et al. (2010) argue, there are some methodological issues associated with twin studies, such as lack of sufficient power or non-additive genetic factors being conflated with shared environment in the classic twin model, that might make it difficult to detect the presence of shared environmental

factors. Furthermore, few twin studies have investigated the relative contribution of genetic and environmental factors to ADHD symptoms in early childhood. Therefore our result may suggest that there is a small amount of shared environmental influences on ADHD symptoms in young children, which might diminish with age, as has been suggested in a previous study on ADHD symptoms in Swedish twins [Larsson et al., 2004]. This pattern has also been observed for other traits, such as general cognitive ability [Haworth et al., 2010], and language skills [Hayiou-Thomas et al., 2012].

Our findings may also suggest that shared environmental factors, such as marital discord, low social class and paternal criminality [Faraone and Biederman, 1997], could influence the association between ADHD symptoms and affective problems, but to a much lesser extent than genetic influences. These findings are in line with the study by Chen et al. (2015), where shared environmental influences were highly influential for the association between ADHD and internalizing problems among 1,316 Chinese twins. On the other hand, shared environmental influences seemed to play negligible role in the studies by Cole et al. (2009), Spatola et al. (2007) and Michelini et al. (2015). This inconsistency might be explained by the different age of study participants, where a potential effect of shared environment might be confined to very young children. However, this needs to be taken with the caveat that these interpretations are based on the model without sex differences, while the model with qualitative sex differences fit data significantly better. In the model with sex differences, there was no significant influence of shared environmental factors on ADHD for girls and on affective problems for boys. This could be due to insufficient statistical power to detect a correlation between two small variance components, or it might indicate that the effect of shared environmental influences on the overlap between ADHD symptoms and affective problems seen in the model without sex differences is a chance finding.

Non-shared environmental factors did not seem to influence the overlap between ADHD symptoms and affective problems in this study. This is consistent with previous studies suggesting that some environmental factors influence ADHD but not affective problems. For instance, low birth weight has been associated with a later risk of ADHD, even when taking genetic and environmental influences into account [Pettersson et al., 2014], but seem to have a weak, if any, impact on depression [Wojcik et al., 2013]. On the other hand, maternal stress during pregnancy have been shown to influence anxiety in offspring, but not ADHD, in a genetically informative study of children born through *in vitro fertilization* [Rice et al., 2010].

We also investigated whether there were any sex differences in the overlap between ADHD symptoms and affective problems. Model fit characteristics did suggest that a model with qualitative sex differences was the best fit, but since the parameter estimates were very similar for boys and girls, with overlapping confidence intervals, it is likely that these differences were probably driven by differences in variance between boys and girls. This is in line with findings from Cole et al. (2009).

Our analyses of the overlap between the two ADHD symptom dimensions and affective problems yielded similar findings to the main analyses – the overlap was almost completely explained by genetic influences for both subtypes of ADHD. This is similar to findings in the study by Michelini et al., where genetic influences explained more than half of phenotypic correlations between inattention and subtypes of anxiety [Michelini et al., 2015]. Unlike their study though, we found significant overlap not only between inattention and affective problems, but between hyperactivity/impulsivity and affective problems as well. This discrepancy might be accounted for by differences in age of study participants or in measures

of affective disorder, as Michelini et al. studied specific subtypes of anxiety separately among adolescents, whereas the affective problems scale used in this study captures depressive symptoms in preschool children.

If these findings extend to clinical groups, then clinicians need to consider the co-occurrence between ADHD and affective problems as early as preschool years. Therefore it is important to assess preschool children referred for ADHD for affective problems as well. The genetic overlap between ADHD and affective problems might furthermore suggest that relatives of children with ADHD might be at a higher risk for affective problems and vice versa, as has been suggested previously [Faraone and Biederman, 1997].

To the best of our knowledge, this twin study is the first to investigate the association between ADHD symptoms and affective problems in preschool children. All twins born in Sweden between January 2004 and May 2005 were contacted in connection with their fifth birthday, with a participation rate of 69.7%. Compared with previous studies, it is clearly a strength that all participants were of the same age. This allowed us to better clarify the association between ADHD symptoms and affective problems during this specific age, which is important given that this association may vary in different developmental periods. Another strength of this study was that ADHD and affective problems were measured with scales developed to be used in questionnaires with parent ratings, and have been shown to have good validity [DuPaul et al., 1998b; Ferdinand, 2008].

There are some limitations that should be taken into account when interpreting the findings from this study. The rather small sample might have resulted in less power to detect statistically significant differences between boys and girls, especially qualitative sex

differences. The sample size also prevented us from performing extremes analyses, which would strengthen the generalizability of findings to clinical settings. However, as twin studies of ADHD generally show similar result in the full sample and at the extreme end of the distribution [Larsson et al., 2012], we believe that the same pattern would emerge at the extremes of our sample. The cross-sectional design of the study prohibits us from drawing conclusions regarding the developmental relationship between ADHD and affective problems. The preschool setting does also induce some limitations as well. It could be difficult to measure both ADHD and affective problems in preschool children as both traits are usually detected and diagnosed at a later age [Faraone et al., 2015; Kessler and Bromet, 2013] and these scales were developed to measure ADHD and affective problems in school-aged children, which is possibly reflected in the relatively low internal consistency for affective problems. It is furthermore possible that the overlap found between ADHD symptoms and affective problems might be partly explained by other traits, such as oppositional defiant disorder [Neuman et al., 2001]. A further consideration regards the generalizability of results from twins to singletons. However, previous studies seem to indicate that twins and singletons are comparable with regard to ADHD symptoms and affective problems [Angold et al., 2002; Moilanen et al., 1999], indicating that it is possible to generalize our results from twins to singletons. Moreover, family studies have shown that relatives of individuals with ADHD have a higher risk of depression, and vice versa, indicating that our findings would likely extend to singletons [Faraone and Biederman, 1997], although these designs are not able to tease apart genetic and environmental influences.

CONCLUSION

In summary, this study shows that there is a significant association between ADHD symptoms and affective problems in preschool children that is mostly explained by genetic influences.

This adds important knowledge to what is currently known about the etiology of both ADHD and affective problems by indicating that these phenotypes are linked from as early as preschool years. This also needs to be taken into consideration when diagnosing young children and clinicians should consider assessing both affective problems and ADHD if one is present. We expect genetic studies of these phenotypes to produce overlapping findings.

Acknowledgements: We thank Dr Ralf Kuja-Halkola for assistance with statistical analysis.

This work was supported by the Swedish Research Council (grant number 2014-3831); the Swedish Research Council for Health, Working Life and Welfare (M.R., grant number 2015-00075); and the European Union's Horizon 2020 research and innovation programme (grant number 667302). HL has served as a speaker for Eli-Lilly and Shire and has received a research grant from Shire; all outside the submitted work. MR and MJT have no conflicts to declare.

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FIGURES

Figure 1. Path diagram showing results from the correlated factors solution of ADHD symptoms and affective problems, (a) separately for boys and girls, and (b) without any sex differences. F=females; M=males; r_A =genetic correlation; r_C =shared environmental correlation; and r_E =non-shared environmental correlation.

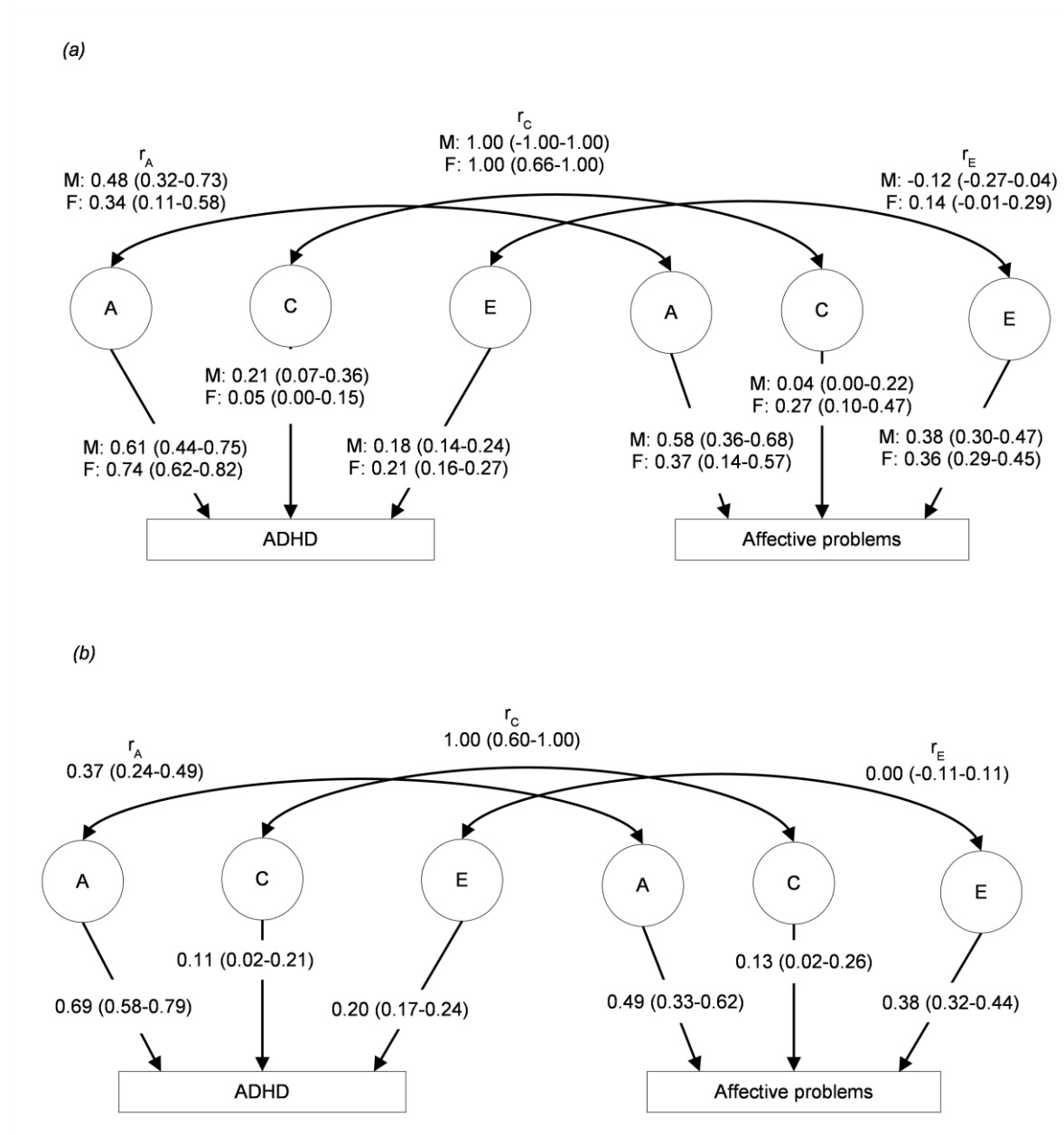


Figure 2. Proportion of the correlation between ADHD symptoms and affective problems in preschool children explained by genetic and environmental influences (shared and unique).

Note: E explained 0.0 % of the phenotypic correlation

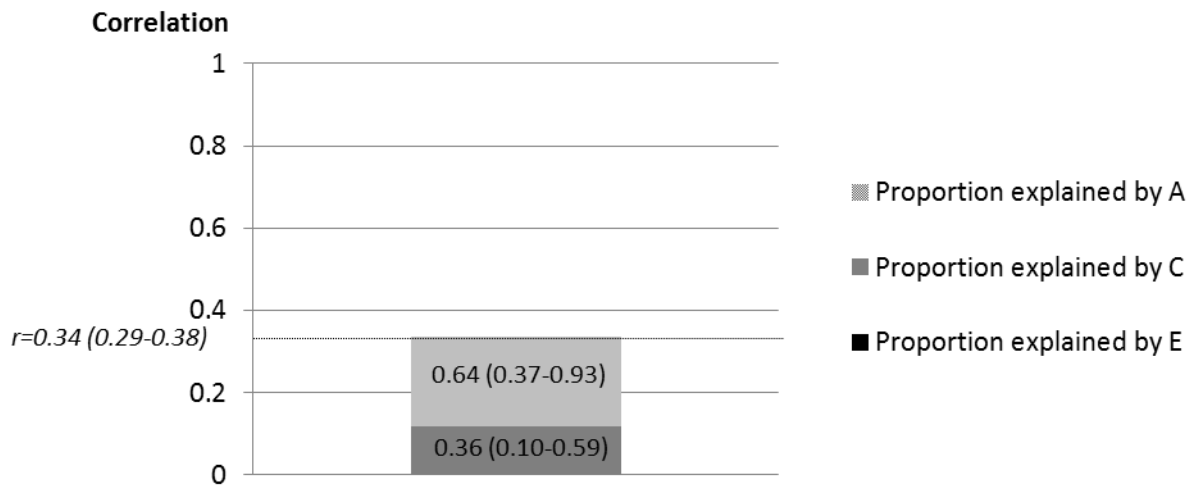
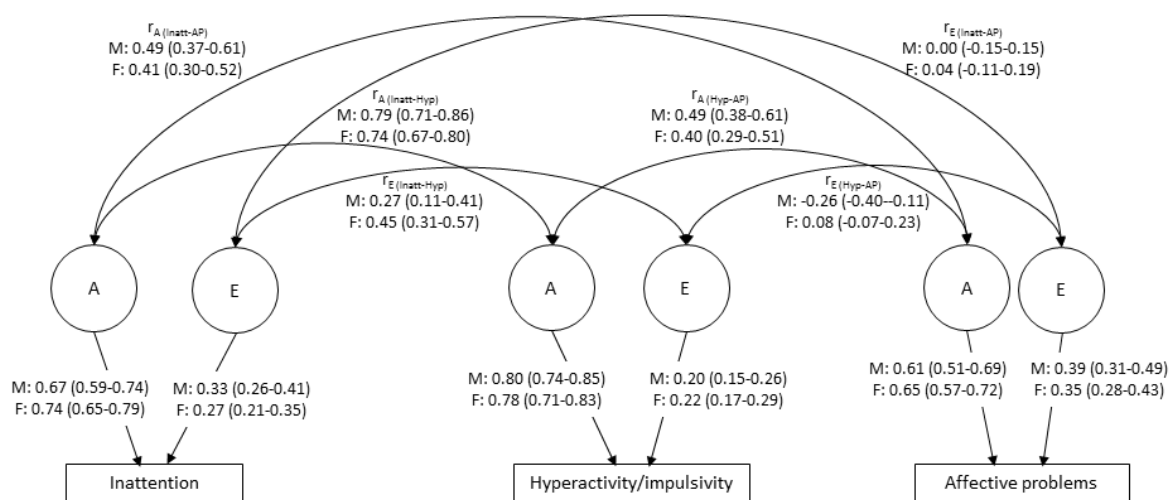


Figure 3. Path diagram showing results from the correlated factors solution of subscales of ADHD and affective problems, separately for boys and girls. Inatt=inattention; Hyp=hyperactivity/impulsivity; AP=affective problems; F=females; M=males; r_A =genetic correlation; and r_E =non-shared environmental correlation.



TABLES

Table 1. Descriptive statistics of the ADHD-scale and the affective problems scale

Measure	Number of items	Skewness ^a	Mean (sd)	Median (IQR)	Min	Max	Chronbach's α^b
ADHD	18	0.70/-0.98	10.54 (6.62)	9.75 (9.50)	0	39.5	0.92/0.92
Affective problems	12	1.85/0.36	1.49 (1.68)	1.00 (2.00)	0	13	0.61/0.64

Sd, standard deviation; IQR, Interquartile Range

^a untransformed data/log transformed data

^b mother rating/father rating

Table 2. Twin correlations and cross-twin cross-trait correlations with 95% confidence intervals for ADHD and affective problems

	ADHD	Affective problems	CTCT between ADHD and affective problems
MZ female	0.77 (0.69-0.83)	0.65 (0.55-0.74)	0.28 (0.14-0.40)
DZ female	0.41 (0.25-0.55)	0.41 (0.25-0.55)	0.22 (0.09-0.35)
MZ male	0.80 (0.73-0.85)	0.60 (0.49-0.70)	0.37 (0.24-0.48)
DZ male	0.47 (0.33-0.60)	0.28 (0.11-0.43)	0.20 (0.07-0.33)
DZ opposite sex	0.45 (0.35-0.53)	0.38 (0.27-0.47)	0.30 (0.22-0.38)

MZ, monozygotic; DZ, dizygotic; CTCT, cross-twin cross-trait correlations.

Table 3. Model fit characteristics for bivariate twin models of ADHD and affective problems

Model	minus2LL	df	AIC
Saturated model	8481.10	3220	2041.10
ACE models			
Quantitative and qualitative sex differences	8521.14	3265	1991.14
Quantitative sex differences	8521.14	3268	1985.14
Qualitative sex differences	8561.23	3276	2009.23
No sex differences	8539.59	3275	1986.59

minus2LL, minus 2 times log likelihood; df, degrees of freedom; AIC, Akaike's information criterion. Best model indicated in bold.

SUPPLEMENTARY TABLES

Supplementary Table 1. Twin correlations and cross-twin cross-trait correlations with 95% confidence intervals for dimensions of ADHD and affective problems

	Twin correlations			CTCT		
	Inattention	Hyperactivity/ impulsivity	Affective problems	Inattention and affective problems	Hyperactivity/impulsivity and affective problems	Inattention and hyperactivity/impulsivity
MZ female	0.73 (0.64-0.80)	0.76 (0.68-0.82)	0.65 (0.55-0.74)	0.25 (0.11-0.37)	0.25 (0.12-0.38)	0.53 (0.43-0.62)
DZ female	0.34 (0.17-0.49)	0.35 (0.18-0.49)	0.41 (0.25-0.55)	0.22 (0.09-0.35)	0.17 (0.03-0.30)	0.31 (0.17-0.45)
MZ male	0.71 (0.61-0.78)	0.76 (0.68-0.82)	0.60 (0.49-0.70)	0.32 (0.19-0.44)	0.37 (0.24-0.48)	0.60 (0.50-0.68)
DZ male	0.34 (0.17-0.48)	0.46 (0.31-0.59)	0.28 (0.11-0.43)	0.18 (0.05-0.31)	0.22 (0.09-0.35)	0.42 (0.29-0.53)
DZ opposite sex	0.39 (0.29-0.48)	0.41 (0.31-0.51)	0.38 (0.27-0.47)	0.25 (0.17-0.33)	0.29 (0.20-0.36)	0.32 (0.23-0.40)

MZ, monozygotic; DZ, dizygotic; CTCT, cross-twin cross-trait correlations.

Supplementary Table 2. Model fit characteristics for trivariate twin models of dimensions of ADHD and affective problems

Model	minus2LL	df	AIC
Saturated model	12001.95	4801	2399.95
ACE model with quantitative and qualitative sex differences	12140.76	4888	2364.76
ACE model with quantitative sex differences	12140.99	4894	2352.99
ACE model with qualitative sex differences	12171.11	4903	2365.11
ACE model without sex difference	12393.99	4927	2539.99
AE model with quantitative sex differences	12163.27	4906	2351.27

minus2LL, minus 2 times log likelihood; df, degrees of freedom; AIC, Akaike's information criterion. Best model indicated in bold.

Supplementary Table 3. Phenotypic correlations between dimensions of ADHD and affective problem, and proportion of correlations explained by genetic and environmental influences

Phenotypic correlation	Males	Females
Inattention and affective problems	0.31 (0.24-0.37)	0.29 (0.23-0.36)
Proportion explained by A	1.00 (0.83-1.19)	0.96 (0.79-1.12)
Proportion explained by E	0.00 (-0.19-0.17)	0.04 (-0.12-0.21)
Hyperactivity/impulsivity and affective problems	0.27 (0.20-0.34)	0.31 (0.24-0.37)
Proportion explained by A	1.27 (1.10-1.49)	0.93 (0.78-1.07)
Proportion explained by E	-0.27 (-0.49--0.10)	0.07 (-0.07-0.22)