Internalizing and neurodevelopmental problems in young people: Educational outcomes in a large population-based cohort of twins

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Abstract

Adolescent internalizing problems such as anxiety and depression have been associated with subsequent educational underachievement. However, it has not been investigated if the association is accounted for by neurodevelopmental disorders (NDDs, i.e., attention-deficit/hyperactivity disorder, autism spectrum disorder, developmental coordination disorder, tic disorder, learning disorder). This study is the first to describe the relationship between internalizing problems at age 15 and educational outcomes in later adolescence while controlling for a wide range of NDDs in childhood, and applying a genetically sensitive design. We used the nation-wide population-based Child and Adolescent Twin Study in Sweden, comprising 4997 fifteen-year-old Swedish twins born between 1994 and 1998. Internalizing problems and NDDs were measured with parental report. Educational outcomes were merit rating and upper secondary education eligibility, retrieved from the National School Register. Internalizing problems at age 15 were found to be negatively associated with educational outcomes in later adolescence. Additive genetics accounted for 89% of the covariation between internalizing problems and merit rating, out of which roughly half were unique genetic effects of internalizing problems and the remaining half due to NDDs. In conclusion, internalizing problems form an important risk factor for subsequent educational underachievement, going beyond the risk conferred by childhood NDDs.

1. Introduction

Internalizing disorders are characterized by depressed mood, anxiety, and related physiological and cognitive symptoms (American Psychiatric Association, 2013). These emotional problems often occur in childhood or adolescence and frequently have been linked to a range of subsequent mental disorders, such as major depression, anxiety disorders, alcohol and drug dependence, and suicidal behavior (Fergusson & Woodward, 2002; Woodward & Fergusson, 2001). In addition, child and adolescent internalizing disorders are associated with educational underachievement later in life (Mojtabai et al., 2015).

Twin studies can be used to disentangle the role of genetic and environmental factors for a trait. The heritability, i.e., the amount of phenotypic variance attributable to genetics, has been found to be moderate in anxiety and depression, around 30 – 40%, while the remaining variance is primarily due to individual factors, referred to as non-shared environment in twin studies (Flint & Kendler, 2014; Hettema et al., 2005). For educational achievement, several studies suggest a heritability of 60% or higher, depending on country, with moderate shared and non-shared environmental influences explaining approximately 20%, respectively (Branigan et al., 2013; Knopik et al., 2017).

Additional to estimating heritability, twin studies also offer a way to determine to what degree an association between two variables is due to common genetic and/or environmental factors. Only a few studies have yet used genetically sensitive designs to investigate the relationship between internalizing disorders (either anxiety and/or depression) and educational outcomes. In 2012, Tambs et al. (2012) examined the relationship between educational level and risk of anxiety disorders in young adult Norwegian twin pairs, using a cross-sectional design. A slightly negative correlation between educational level and anxiety disorders was reported, which was primarily caused by genes common to the two traits. Lewis et al. (2017) examined the genetic and environmental influences on parental ratings of behavioral problems...
(defined as anxiety, hyperactivity, conduct problems, and peer problems) across childhood and adolescence as predictors of educational achievement at age 16. Educational achievement was predicted by both shared environmental influences on anxiety, and genetic influences on externalizing behavior, i.e., conduct problems and hyperactivity in childhood. Finally, in 2018, the Brainstorm Consortium reported a substantial and significant negative genetic correlation between college attainment, years of education, and anxiety disorders (Anttila et al., 2018).

While most findings refer to the specific effects of childhood or adolescent internalizing disorders on subsequent educational achievement, lesser is known about the possible confounding role of neurodevelopmental disorders (NDDs, i.e., attention-deficit/hyperactivity disorder [ADHD], autism spectrum disorder, developmental coordination disorder, tic disorder, and learning disorder). NDDs are a group of disorders which have their onset in the developmental period, and are characterized by deficits leading to impairment of personal, social, academic, or occupational functioning (American Psychiatric Association, 2013). NDDs and traits of NDDs are generally stronger predictors of educational failure (Howlin et al., 2013; Loe & Feldman, 2007) than internalizing disorders, and the coexistence between the disorders is substantial (e.g., Bauermeister et al., 2007; Kerns et al., 2014; Luby et al., 2003; Simonoff et al., 2008). Taken together, it is plausible that the association between internalizing problems and educational achievement is affected by the presence of childhood NDDs. We therefore hypothesize that NDDs will exhibit a large influence on the association between internalizing problems and educational achievement, and contribute substantially to the etiological influence on the association between internalizing problems and educational achievement. To our knowledge, this is the first study to describe the relationship between youth internalizing problems and educational achievement in later adolescence in a genetically sensitive design, while also controlling for NDDs. The specific aims in this population-based study of 4997 Swedish twins were to (1) assess the association between parental reported internalizing problems at age 15 and educational achievement from service-based registers, and to test whether NDDs assessed in childhood confound a possible association. (2) Employ multivariate twin analyses to examine the genetic and environmental contributions to any associations found.

2. Method

2.1. Participants

Two data sources were merged to examine the relationship between internalizing problems at age 15 and educational achievement in later adolescence: The Child and Adolescent Twin Study in Sweden (CATSS) and the National School Register (The Swedish National Agency for Education, 2020). CATSS is an ongoing, longitudinal, population-based study of twins (for details, see Anckarsäter et al., 2011). Briefly, since 2004, parents of all Swedish twins born from July 1992 and onwards are contacted in connection with the twins’ 9th or 12th birthday (CATSS-9/12) and asked to participate in a telephone interview, which includes measures of, among other things, NDDs. When the twins reach the age of 15 (CATSS-15), families are contacted again and asked to fill out a web-based questionnaire, targeting various mental health problems and social milieus. CATSS-15 includes twins born from the first of January 1994 up until 2002.

2.2. Measures

2.2.1. Internalizing problems at age 15

CATSS-15 includes the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). The SDQ is a brief, 25-item behavioral screening questionnaire for children and adolescents between 3 and 16 years, and was developed to assess externalizing and internalizing problems. It consists of five subscales (i.e., conduct problems, hyperactivity, emotional symptoms, peer problems, and prosocial behavior) with five items in each subscale. In the present study, the emotional problems scale, parental report, was used as an indicator of internalizing problems. The scale has 5 items with 3 response options: 0 (not true), 1 (somewhat true), and 2 (certainly true), yielding a total score between 0 and 10. The SDQ is widely used to screen for internalizing problems both in community and clinical settings (Gustafsson et al., 2017). Studies of the Swedish version of the SDQ symptom scales have confirmed the factor structure of the original English SDQ (Smedje et al., 1999), and results from a validation study of the Swedish SDQ indicate that the parental version discriminates well between psychiatric and non-psychiatric individuals (Malmberg et al., 2003).

2.2.2. Neurodevelopmental disorder proxies

The Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC; Hansson et al., 2005) is included in CATSS-9/12. The A-TAC is a fully structured 96-item parent-report telephone interview designed for large-scale epidemiological purposes. A-TAC is based on symptom criteria and common clinical features of common child and adolescent psychiatric disorders. Items are scored as 1 (yes), 0.5 (yes, to some extent), and 0 (no) and are divided into modules corresponding to diagnostic domains. Distributions, Cronbach’s α and heritability estimates are reported elsewhere (Anckarsäter et al., 2011). Cross-sectional and longitudinal validation studies show good to excellent predictive validity for, amongst others, ADHD, autism spectrum disorder, developmental coordination disorder, tic disorder, and learning disorder (Larson et al., 2010; Mårland et al., 2017). A study by Pettersson et al. (2013) reported that a broad NDD factor accounted for a large proportion of the covariation among NDD problems. In order to control for the presence of NDD symptoms as well as their extensive phenotypic overlap, both above and below diagnostic thresholds, we performed a factor analysis of the 53 items on the A-TAC targeting ADHD, autism spectrum disorder, developmental coordination disorder, tic disorder, and learning disorder to examine their latent structure. We fitted a one-factor model and created a single factor score for each individual that we subsequently included as a covariate in the regression analyses/ as a variable in the multivariate twin analyses.

2.2.3. Educational achievement in later adolescence

A personal identification number is assigned to all individuals living in Sweden, either at birth or upon receiving citizenship. This enables linkage across health and service registers. The National School Register contains data on the highest attained education by calendar year for all individuals aged ≥ 15 years since 2010. Registration in Swedish regist- ters such as the School Register is mandatory, thereby reducing attrition and selection bias. In the present study, we retrieved data on merit rating (a composite score ranging from 0 to 320 where 320 denotes the highest possible grade in all subjects; approximately similar to a grade point average), and upper secondary education eligibility for all participants, defined as completion of compulsory school, with passing grades in English, Mathematics and Swedish or Swedish as a second language. Linkage to data was updated until the 31st of December 2013. A total of 4997 individuals born between 1994 and 1998 whose parents had responded in CATSS-9/12 and CATSS-15 were included, out of which 29.1% were monozygotic (MZ) twins, 63.5% were dizygotic (DZ) twins, and for 7.4% the zygosity could not be determined. Only MZ and DZ twins where information was available from both twins in a pair were used in the multivariate twin analyses, resulting in 1426 MZ and 3044 DZ individuals, or a total of 4470 twins.

2.3. Statistical analyses

2.3.1. Regression analyses

To assess the relationship between internalizing problems at age 15 and educational achievement in later adolescence, we (1) used linear
regression models on the continuous outcome (merit rating) as dependent variable, and the total score of internalizing problems as the independent variable. Results are presented as regression coefficients, i.e., the increase in merit rating (range 0-320) per unit increase in the exposure. (2) We used logistic regression models to regress the categorical outcome (upper secondary education eligibility) on internalizing problems. Results are presented as odds ratios (OR), i.e., comparing the odds of the outcome in the exposed and unexposed group. Unadjusted models are controlled for sex only, while adjusted models are controlled for sex and the general NDD factor to test for confounding of NDD symptoms in childhood. Additionally, we carried out analyses where we neither controlled for sex nor the NDD factor (full crude models), and where we only controlled for the NDD factor. We did this both for all individuals, as well as sex specific (estimates of additional analyses can be found in Supplementary Table 1). A cluster-robust sandwich estimator was applied to adjust the standard errors for the nested twin data. P < 0.05 was considered statistically significant.

2.3.2. Correlations
To assess familial similarity in childhood NDD symptoms, internalizing problems at age 15, and educational achievement in later adolescence, we estimated correlations across these traits within and between twins in a pair. We did this separately for MZ and DZ twins. Since MZ twins are genetically identical, while DZ twins share, on average, 50% of their co-segregating alleles, a higher correlation in MZ-pairs than DZ-pairs are a first approximation of whether there are genetic contributions to a trait, as well as to the association between traits. Correlations between traits, within individuals, are referred to as phenotypic correlations; correlations between the same trait across twins as intra-class correlations; and, correlations across twins and across traits as cross-twin cross-trait correlations. Correlations between continuous variables (general NDD factor, internalizing problems, and merit rating) were calculated as Pearson correlations, correlation between binary variables (upper secondary education eligibility) as tetrachoric correlations, and correlations between continuous and binary variables as biserial correlations.

2.3.3. Multivariate twin modelling
Quantitative genetic models were fitted to estimate contributions of additive genetics (A), shared environment (C; non-genetic contributions to similarity between twins in pairs), and non-shared environment (E; contributions to dissimilarity between twins in pairs) to the variance and covariances within and between twins. This was done by fitting structural equation models with latent factors: additive genetic sources of variance and covariance, assumed to correlate 1.0 between MZ twins and 0.5 between DZ twin (A); shared environmental sources of (co)variance, assumed to correlate 1.0 between MZ and between DZ twins (C); and non-shared environmental sources of (co)variance, assumed to correlate 0.0 between twins in pairs (E). We fitted two ‘trivariate’ models, with the general NDD factor, internalizing problems, merit rating or upper secondary education eligibility, while also controlling for sex and birth year. Cholesky decomposition models were used to determine which A, C, and E-sources that can explain variance and covariance between variables (see illustration in Fig. 1). The models were set up so that A, C, and E-sources of the general NDD factor could explain variance in, and covariance between, internalizing problems and merit rating/upper secondary education eligibility, while not vice versa. We then calculated the explained covariance between internalizing problems and merit rating/upper secondary education eligibility due to A, C, and E-sources from the general NDD factor, as well as the same sources not explained by this factor. Note that A, C, and E contributions to covariance are not constrained to be in the same direction as the total phenotypic covariance. Thus, when calculating explained relative contributions to covariance, defined as each contribution divided by the total covariance, the sum will always be 1, but all contributions do not have to be positive for all separate A, C, and E-sources of covariance. As a result, sums of subsets of contributions (e.g., only A contributions) may be greater than 1.

All analyses were carried out in R 3.6.1 (R Core Team, 2019). Regression analyses were conducted using the ‘gee’ function from the R package ‘drgee’ (Zetterqvist & Sjölander, 2015). Estimation of observed correlations and structural equation modeling were executed via the R package ‘OpenMx’ (Neale et al., 2016).

Fig. 1. Trivariate Cholesky decomposition model for neurodevelopmental disorder symptoms, internalizing problems, and educational achievement. Note. NDDs = general neurodevelopmental disorders factor. INT = Internalizing problems at age 15. The figure depicts the variation and covariation within one twin individual, but in model-fitting the covariance across the twins in pairs were also included.
3. Results

3.1. Descriptives

Descriptive statistics for sample variables and scales are presented in Table 1. The mean score on internalizing problems at age 15 was 1.07 (SD = 1.53). Merit rating had a mean of 231.46 (SD = 54.57). Of all individuals, 94.5% were eligible for upper secondary education.

3.2. Regression analyses

Table 2 shows the associations between internalizing problems at age 15 and educational outcomes in later adolescence, as well as the number of individuals available in each analysis. For merit rating, each increasing step on the total score of internalizing problems corresponded to a decrease of 6.77 (95% CI 8.03 – 5.50) points in merit value. The association stayed statistically significantly different from 0, also after adjusting for the general NDD factor. For upper secondary education eligibility, the adjusted OR was 0.80 (95% CI 0.74 – 0.87). Supplementary Table 1 contains estimates for additional models: fully crude (i.e., neither controlled for sex nor NDD symptoms), adjusted for only NDD symptoms, as well as sex stratified analyses (fully crude and only adjusted for NDD symptoms).

3.3. Multivariate twin analyses

Phenotypic correlations and model fit statistics are available in Supplementary Table 2. Observed intra-class and cross-twin cross-trait correlations for MZ and DZ twins can be found in Table 3. Correlations were higher for MZ than for DZ twins for all intra-class and cross-twin cross-trait correlations, indicating genetic influences on all traits and on all association between traits.

Fig. 2 depicts the correlation between internalizing problems and merit rating/upper secondary education eligibility, decomposed into contributions from A, C and E. The correlation is further decomposed into contribution that could be explained by the general NDD factor, and contributions that were not explained by the general NDD factor and thus unique to internalizing problems and the educational outcome. Additive genetics accounted for .89 of the covariance between internalizing problems and merit rating, of which .49 (95% CI .25 – .72) were unique genetic effects of merit rating and internalizing problems (i.e., not explained by the general NDD factor; see Table 4). The corresponding figure for upper secondary education eligibility was 1.19 (above 1, since the C from the general NDD factor contributed to the association in the opposite direction), of which .67 (95% CI .14 – 1.20) were unique genetic effects of upper secondary education eligibility and internalizing problems. The path coefficient estimates from the Cholesky models for the two educational outcomes can be found in Supplementary Figures 1 and 2.

### Table 1

Descriptive statistics for sample variables and scales. Absolute number of individuals N (%) = 4997 (100).

| Variable                          | Mean (SD) | n (%) |
|----------------------------------|-----------|-------|
| Internalizing problems           | 1.07 (1.53)|       |
| Merit rating                     | 231.46    | (54.57)|
| Upper secondary education eligibility | 4724     | (94.5)|
| Sex                              | 2435      | (48.7)|
| Zygosity                         |           |       |
| Monozygotic                      | 1455      | (29.1)|
| Dizygotic                        | 3171      | (63.5)|
| Birth year                       |           |       |
| 1994                             | 1250      | (25.0)|
| 1995                             | 1238      | (24.8)|
| 1996                             | 1139      | (27.2)|
| 1997                             | 1139      | (27.2)|
| 1998                             | 11 (0.2)  |       |

### Table 2

Associations between internalizing problems at age 15 and educational outcomes, and number of individuals in each analysis. Estimates (95% confidence intervals).

| Educational outcome | Internalizing problems |
|---------------------|------------------------|
|                      | N          | Unadjusted | N          | Adjusted* |
| Merit rating         | 4997       | –6.77 (-8.03 – 5.50)| 4258       | –5.34 (-6.71 – 3.96) |
| Upper secondary      | 4997       | 0.77 (0.72 – 0.82) | 4258       | 0.80 (0.74 – 0.87) |

* Adjusted for general neurodevelopmental disorders factor at age 9/12.

†† Expressed as regression coefficient.

### Table 3

Intra-class and cross-twin cross-trait correlations and 95% confidence intervals for childhood neurodevelopmental disorder symptoms, internalizing problems at age 15, merit rating, and upper secondary education eligibility, adjusted for sex and birth year. Bold estimates on the diagonal represent intra-class correlations (MZ/DZ); MZ cross-twin cross-trait estimates are below the diagonal, DZ cross-twin cross-trait estimates are above the diagonal.

| NDDs | INT | Merit rating | Upper education |
|------|-----|--------------|-----------------|
| NDDs | .65 (.62 – .69) | .13 (.10 – .16) | .12 (.16 – .08) | .02 (.10 – .07) |
| INT  | .23 (.19 – .28) | .47 (.42 – .52) | .22 (.19 – .26) | .11 (.15 – .07) | .08 (.16 – .01) |
| Merit rating | .24 (.31 – .18) | .14 (.20 – .08) | .90 (.89 – .92) | .61 (.57 – .64) |
| Upper education | .34 (.44 – .24) | .18 (.28 – .07) | .96 (.93 – .99) | .64 (.53 – .75) |

Note. NDDs = General neurodevelopmental disorders factor. INT = Internalizing problems at age 15. Upper education = Upper secondary education eligibility.

* Upper secondary education eligibility is dependent on merit rating, why no correlation is presented.

4. Discussion

In this longitudinal, population-based twin study, internalizing problems at age 15 were found to be negatively associated with educational outcomes in later adolescence. This association was still statistically significant even after adjusting for a range of earlier assessed NDD symptoms. This provides robust evidence that youth...
internalizing problems such as anxiety and depression represent an independent risk factor for subsequent educational achievement and opens up for the possibility that a reduction of internalizing problems in adolescence may improve educational achievement, even in the presence of NDDs. Nonetheless, multivariate twin analyses indicated an equally large contribution from NDDs to the association between internalizing problems and educational outcomes, which is not surprising given that NDDs are indicative of internalizing problems such as anxiety and depression (Mayes et al., 2011; Peterson et al., 2001).

However, it is reasonable that the treatment of NDDs in childhood may indeed affect trajectories leading to the development of internalizing problems (Golubchik et al., 2017; Snircova et al., 2016), therefore possibly mitigating both internalizing problems and educational underachievement later in life. For example, in a study by Lu et al. (2017), students with ADHD had higher scores on higher education entrance tests if they were taking ADHD medication at the time, compared to times they were not on medication, suggesting that ADHD medication may improve educational outcomes in individuals with ADHD. Our results suggest that interventions targeted towards educational outcomes in adolescence should consider both NDDs and internalizing problems, i.e., it is not internalizing problems or NDDs that explain educational underachievement.

Internalizing problems were influenced by moderate-to-large genetic and non-shared environmental influences. The educational outcomes were roughly two-thirds due to genetic and one-third due to shared environmental influences, which has been mirrored in several other studies (Branigan et al., 2013; Flint & Kendler, 2014; Hettema et al., 2005; Knopik et al., 2017). The phenotypic association between internalizing problems and educational outcomes was mainly attributed to genetic factors. These findings are in accordance with results from Tambs et al. (2012) and Lewis et al. (2017), albeit the latter found that shared environmental influences on anxiety in childhood were
predictive of educational achievement at age 16. This discrepancy might reflect rater bias, and/or that anxiety in childhood differs in its presentation compared to adolescent anxiety, e.g. children are more likely to be diagnosed with separation anxiety disorder than adolescents who were more frequently diagnosed with social anxiety disorder (Waite & Creswell, 2014). In line with this is that anxiety and depression symptoms appear to differ in their phenotypic and genetic structure in childhood, adolescence and young adulthood (Waszczuk et al., 2014). Furthermore, we found a large genetic contribution to the association between internalizing problems and educational outcomes that was due to the general NDD factor. This indicates that the same genetic factors that influence NDDs also affect internalizing problems and educational achievement, which is in line with the emerging concept of a common underlying susceptibility for nearly all mental disorders (Caspi et al., 2014; Caspi & Moffitt, 2018).

The study has several strengths, including use of a longitudinal, population-based, genetically sensitive design, large sample sizes, high response rates, and validated assessment instruments. The linkage to a nation-wide register is an additional advantage, offering up the possibility to analyze internalizing problems and educational outcomes with little or no shared method variance.

The findings also have to be interpreted in the light of some limitations. Even though registration in the National School Register is mandatory, we were not able to obtain educational information on the whole sample. This applies to individuals who have not reached the age of inclusion into the National School Register (younger than 16 years if they were born before 2010). Furthermore, individuals who dropped out of school before merit rating and upper secondary education eligibility were assessed are not included into the register, i.e., those with possibly more profound mental health issues, are not included into the analyses. Related to this, we only assessed internalizing problems at age 15 and merged individuals to their data at age 9/12, which resulted in an attrition rate of 43%. Thus, results should be interpreted with some caution regarding generalizability, i.e., individuals whose parents did not respond might have a more profound neurodevelopmental or internalizing symptomatology. Finally, the fact that internalizing problems were rated by parents only may have led to an underestimation of the rate of such problems in the twins (Achenbach et al., 1987; Kazdin et al., 1983).

Declarations

Ethics approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The CATSS (including the National School Register) is approved by the Ethical Review Board at Karolinska Institutet (Dnr 02-289; 03-672; 2010/597-31/1; 2009/739-31/5; 2010/1410-31/1; 2015/1947-31/4).

Authors' contributions

RKH, SL and SD designed the study. SD performed all statistical analyses. SD and SL wrote the manuscript. RKH, PL, and CG critically read and revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets are available on reasonable request from the corresponding author at sabrina.doering@gu.se.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.psychres.2021.113794.

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