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Title: The relationship of school performance and mental health:
Educational achievement as indicator of psychopathology

Author: Wendelina (Wanda) Meta Tempelaar

ISBN: 978-94-028-0818-6

Cover design by Bas van Kesteren & Elemi Breetvelt

Layout: WM Tempelaar, EJ Breetvelt

Printed by: Ipkskamp

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The studies described in this thesis were performed at the Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Center Utrecht, Utrecht, the Netherlands

**The relationship of school performance and mental health:
Educational achievement as indicator of psychopathology**

De relatie tussen schoolprestaties en geestelijke gezondheid:
Onderwijsvoortgang als indicator voor psychopathologie

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van
de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het
college voor promoties in het openbaar te verdedigen op donderdag 21 december
2017 des middags te 2.30 uur

door

Wendelina Meta Tempelaar
geboren op 15 februari 1982 te Groningen

Promotoren: Prof.dr. R.S. Kahn
Prof.dr. M.H.J. Hillegers

Copromotor: Dr. M.P.M. Boks

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1

General introduction and outline

INTRODUCTION

Mental health problems are common, persistent and disabling. According to the World Health Organization (WHO) the global prevalence of lifetime mental disorders in adults is estimated at 18.1-36.1%¹. The 12-month prevalence estimate is 9.8-19.1%¹. Many mental disorders have large adverse effects on general functioning including domains of social, educational, occupational and financial life. The disability burden of mental disorders is immense and improvement is urgently needed. Subsequently costs of mental health services are enormous and the impairments associated with mental disorders are that large that WHO estimated interventions could have positive cost-effective ratios, from both societal and employer perspectives¹. In the Netherlands the prevalence of mental disorders in the general adult population is high: the prevalence 'ever' of all disorders was 42.7%, the 12-month prevalence 18.0% (NEMESIS-2)². Approximately a quarter of Dutch adolescents (21.5%) suffer from a mental disorder³ and even more have general mental health problems^{4,5}. Mental health problems are strongly associated with psychiatric disorders⁶ and compromise daily functioning^{4,7}. Mental health problems in childhood and adolescence can have major adverse effects on development that may persist lifelong⁸. In fact, many "adult" psychiatric disorders begin during childhood or adolescence and progress throughout the years⁹.

Early identification is of great importance since early interventions may ameliorate, delay, or even prevent illness progression and ultimately result in improved daily functioning^{10,11}. However, identifying those at risk for mental disorders is difficult. For instance, early symptoms of schizophrenia, one of the most severe psychiatric disorders, typically start during adolescence or early adulthood and progress through life. These early symptoms are often heterogeneous and overlap with symptoms of other psychiatric disorders. Risk factors associated with an increased risk for developing schizophrenia also overlap with risk factors for other psychiatric disorders.

In recent years there have been many attempts to identify individuals and groups at high risk for development of severe mental illness, often based on attenuated or brief psychotic symptoms and/or a family member with severe mental illness. However, a large portion of the patients with mental illness such as schizophrenia may not go through the same trajectory of early psychotic symptoms or have an affected family member. So the search for risk markers to screen for early identification continues. These include bio-markers, neuroimaging markers and genetic markers.

However, most of these are not yet easily applicable in the general population because of the burden they put on the risk population (children and adolescents), either directly at the individuals or indirectly in costs. Educational achievement may be an obvious potential factor to indicate groups at risk for mental illness, since educational achievement has been related to mental health problems and severe psychiatric disorders such as schizophrenia¹². In the Netherlands and in most Western countries, the vast majority of children and adolescents attend school and are subsequently monitored in their individual educational achievement. This monitoring is done as a standard element of the curriculum and no additional burdens or costs are associated. Educational achievement is monitored on a structured, well-defined manner and applied to all pupils continuously during their entire schoolcareer. Moreover, screening for severe psychopathology would ideally take place in childhood and adolescence, which corresponds perfectly with obliged primary and secondary education. In the Dutch educational system, poor educational achievement is already a common reason for referral to a school doctor or general practitioner. But pupils who underachieve constitute a heterogeneous group since poor educational achievement may be a symptom of cognitive, emotional or social difficulties. Some pupils who have poor grades at school suffer from mental health problems, but certainly not all of them have or develop a severe mental illness. It is of interest whether educational achievement can be used as an early indicator and possible selection of individuals and groups at risk of mental illness. While more and more is known on educational achievement in relation to psychopathology, especially in schizophrenia, several questions remain. Investigating the exact relationship between educational achievement and mental health problems and development of psychiatric disorder is of importance to further investigate the potential value of educational achievement as an indicator of individuals and groups at risk for psychopathology.

The studies in this thesis were set out to further explore the association between poor educational achievement and psychopathology.

What is known?

Most research on the relationship between educational achievement and psychiatric disorders has focused particularly on schizophrenia since a large body of literature showed that cognitive impairment is a core feature of schizophrenia and educational achievement can be viewed as a practical indicator of cognitive functioning¹³.

Cognition, intelligence and educational achievement

Cognition, intelligence and educational achievement are all related in a complicated way. To gain more understanding of these relationships it is important to define these terms.

- Cognition is generally considered any measure of cognitive performance, such as attention, memory, processing speed and reasoning¹⁴.

- Intelligence can be described as the ability to acquire, retain and apply knowledge and skills¹⁵. Intelligence is generally measured in Intelligence Quotient (IQ) tests.

- Educational achievement is considered all performances at school, ranging from grades, standardized exams, or levels pupils perform in. Poor educational achievement can take many forms, such as repeating a grade, school dropout, low grades or functioning at a lower than expected scholastic level (based on familial cognitive aptitude or teachers expectation).

Cognition overlaps with intelligence. Intelligence is known to be a strong predictor of educational achievement but besides IQ other factors are also important for educational achievement^{16,17}.

From an etiologic point of view IQ can be seen as a confounding factor in the relationship between educational achievement and psychopathology. This might be due to shared genetic factors. Development of psychiatric symptoms and intelligence may be influenced by genes impacting on brain functions including both cognition and symptoms of psychopathology.

Schizophrenia and cognitive impairment

Multiple cognitive domains are impaired in schizophrenia, including IQ, memory and executive functions^{18,19}. Numerous studies described the characteristics and course of these cognitive impairments¹⁹⁻²¹. Regarding the impairment in IQ, the course of the deficit tends to stay relatively moderate on a group level but there is a vast amount of variability between patients, suggesting there may be subgroups of patients that differ on onset, severity and progression of cognitive impairment²²⁻²⁴. In general the onset of cognitive deficits is in childhood or adolescence, well before onset of psychotic symptoms^{22,25}. This impairment remains relatively independent of psychotic symptoms^{26,27} and mild deficits are also found in unaffected first-degree relatives²⁸.

These findings suggest that cognitive impairments are likely intrinsic to schizophrenia and have been suggested as potential markers of the disease and its progression²⁹.

Schizophrenia and educational achievement

Poor educational achievement is associated with increased risk for schizophrenia^{12,30-32}. Lower performances on formal tests, low grades and grade retention have been related to later development of schizophrenia³¹⁻³⁴. Deviation in expected scholastic achievement based on familial cognitive aptitude is also a strong predictor of later development of schizophrenia¹². In addition, unaffected offspring of schizophrenia patients show poorer educational performance than healthy controls³⁰. While educational achievement may deteriorate because of (early) psychotic symptoms these findings occur well before average illness onset. Thus poor educational achievement may reflect neurodevelopmental impairments in schizophrenia and also act as an early marker for this disorder.

Cognition and educational achievement in other psychiatric disorders

Cognitive deficits were considered specifically related to schizophrenia but in the last decades several studies have reported lower IQ and neuropsychological impairments in patients with bipolar disorder, although results are equivocal and it is not clear yet whether this is a result of the illness, medication or other factors³⁵⁻³⁷. A recent meta-analysis of premorbid IQ showed no decline in bipolar patients compared with schizophrenia patients and unaffected controls³⁸. On the other hand, it has recently been suggested that subtle neuropsychological impairment may exist prior to illness onset³⁹. Findings on educational achievement in bipolar disorder are inconsistent; poor scholastic achievement has been related to development of bipolar disorder^{12, 40, 41} and higher risk for termination of schooling⁴². Interestingly, some studies showed also normal or superior educational achievement prior to the onset of bipolar disorder^{35,40}. Few studies investigated cognitive deficits in other psychiatric disorders. Severe depression and anxiety disorder appear related to lower IQ^{43,44}. Regarding educational achievement, general population studies show that in general 10% of high school drop-out was related to psychiatric disorders⁴² and 5% in college⁴⁵. Moreover, in studies with children and adolescents during their schoolgoing years it is shown that psychiatric disorders are related to underachievement at school. For instance anxiety disorders, substance use disorders and externalizing disorders are related to increased school drop-out^{46,47}. Internalizing disorders such as adolescent depression are associated with poorer grades^{48,49}. ADHD is also associated with poorer grades and with increased grade retention and low rates of secondary school graduation as well⁵⁰.

Socio-demographic factors

Socio-demographic factors that could influence both psychopathology and educational achievement are socio-economic status, urbanicity and traumatic experiences^{17,51,52}. Cannabis use also is associated with impaired cognitive functioning and increased risk for schizophrenia⁵³. Other factors such as obstetric/perinatal complications and some infections can also influence the association between psychopathology and cognition⁵³.

Outline:

In the first part of this thesis we studied the characteristics of poor educational achievement as a possible risk indicator for psychopathology. We investigated the relationship between poor educational achievement in adolescents at secondary school and general mental health problems in collaboration with the Public Health Centre. We defined poor educational achievement when children were not in their normal grade at school. We studied two types of poor educational achievement at secondary school: grade retention (**chapter two**) and downgrading (chapter three). In chapter two we investigated whether poor educational achievement was a risk indicator by itself and focused on the confounders in the relationship between delayed school progression and general mental health problems measured with the Strengths and Difficulties Questionnaire (SDQ).

In **chapter three** we further investigated the relationship between poor educational achievement at secondary school and general mental health problems. We examined the role of school factors in more detail, the interaction with poor educational achievement and whether there are certain subgroups in the group of pupils with poor educational achievement.

In **chapter four** we examined in more detail whether poor educational achievement is specifically related to certain severe psychiatric disorders. We assessed lifetime educational achievement and investigated the association with schizophrenia, bipolar disorders and depression. We also reported on familial vulnerability to these severe psychiatric disorders and educational achievement.

In **chapter five** we investigated the relationship between educational achievement, cognition and psychopathology exclusively in offspring from parents with bipolar disorder. Less is known on the relationship between bipolar disorder and cognition and educational achievement and even fewer studies investigated educational achievement and cognition in an at-risk population for bipolar disorder. In this study we examined general cognitive ability and poor educational achievement (a decline in educational track, grade retention and/or early school termination) in a longitudinal course from adolescence onward. We studied the association with psychopathology and influence of other factors such as age of onset concurrently.

The Dutch school system consists of eight years of primary education, four to six years of secondary education and two to six years of higher education. Education is common but eligible at 4 years, and compulsory from 5 years onwards until the age of 16. State schools provide almost all primary and secondary education. In primary school (age 4-12), all children are educated at the same level.

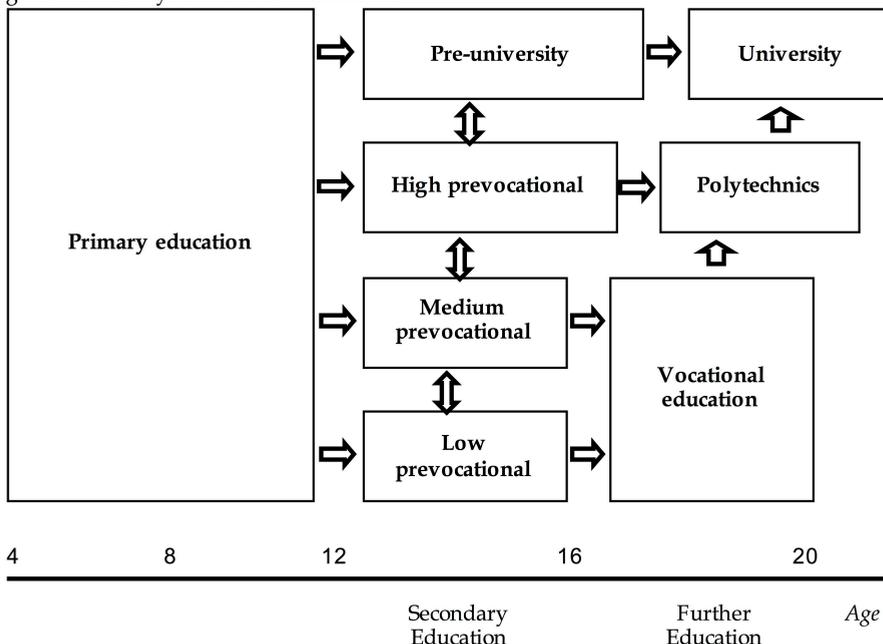
At the end of primary school, all pupils take a standardized national exam to test their aptitude at age 11-12 years. Their primary school teacher refers them to their starting track at secondary school based on their results on the exam and the child's entire primary school record. (At the time our studies were executed most pupils would be monitored in a standardized national exam, the 'school readiness test', which tests skills in reading, arithmetic and study skills. In the last few years the monitoring system has been extended with a longitudinal pupil monitoring system, in which pupils are frequently assessed (at least yearly) on reading, arithmetic and basic skills. The teacher can use these results to optimize the pupil's education on their personal needs.)

In secondary school (starting at age 12), children can attend different tracks of education (apart from special education): low ('VMBO-basis/kader'), medium ('VMBO-GL/TL') and high prevocational ('HAVO') and pre-university ('VWO') education. Some secondary schools provide so-called combination classes, in which pupils can work at the level of two consecutive tracks, to provide the opportunity for pupils to experience both tracks when there is doubt about the appropriate educational level.

During their school career all pupils can retain a grade or either downgrade or upgrade in tracks according to their actual performance at school.

At the end of secondary school, all pupils take national state exams at their respective level and can enter further education in the three follow-up tracks: vocational education (nationwide 54% of all pupils), polytechnics (28% of all pupils) or university (18% of all pupils).

Figure 1: School system in the Netherlands



Risk

Risk is the probability that an event will occur. In research it is mostly used to express the probability that a certain outcome will occur following a certain exposure.

The term risk factor is generally used for a variable that is statistically related to an outcome and mostly used when describing a causal relationship.

The term risk marker or risk indicator is mostly used for a variable that is associated with increased probability (of a disease), but is not necessarily a causal factor.

Confounding factors

In epidemiology, prognostic and etiologic research designs are discerned. In etiologic research focus is usually on causation; the factors coming together to cause an illness. Confounding factors are then an important aspect to acknowledge. Confounders are defined as variables that influence the independent and dependent variable, in other words: the outcome (disease) and the exposure variable.

From an etiological viewpoint confounding is important to understand the causal pathway leading to development of illness. From a more practical point of view when looking for risk markers it is less important whether particular factors are part of the causal pathway, as long as they are associated with increased probability of development of the illness.

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2

Delayed school progression and mental health problems in adolescence: a population-based study in 10,803 adolescents

Wanda M. Tempelaar MD, Christiaan P. Otjes MD, Clothilde J. Bun MSc, Carolien M. Plevier MSc, Willemijn A. van Gastel PhD, James H. MacCabe MD PhD, René S. Kahn MD PhD, Marco P. Boks MD PhD

BMC Psychiatry, 2014 September 14; 14:244

ABSTRACT

Background: Accumulating evidence suggests that several adult mental disorders, particularly psychoses, are preceded by impairments in cognitive function, reflected in scholastic underachievement. This study investigates the association between scholastic underachievement and general mental health problems in adolescence, using delay in school progression as a marker of poor scholastic performance.

Method: Cross-sectional secondary school survey comprising 10,803 adolescents. Participants completed the Strengths and Difficulties Questionnaire (SDQ) to assess mental health problems. The association of delayed school progression with the SDQ was investigated using logistic regression with SDQ as outcome and delayed school progression as primary exposure of interest while adjusting for socio-demographic characteristics, adverse life events, school-related factors, risk taking behaviour, healthy lifestyle and physical health.

Results: Unadjusted analysis showed an association between delayed school progression and total mental health problems (OR 1.83, 95% CI 1.27 - 2.63) in adolescents. After adjusting for other risk factors (socio-demographic factors and life events) in a logistic regression model the association between delayed school progression and mental health problems was attenuated (OR 1.33, 95% CI 0.86 - 2.05).

Conclusion: Delayed school progression is associated with general mental health problems in adolescence, but this relationship is heavily confounded by other factors. A causal relationship between impaired cognitive function such as poor scholastic performance and general mental health at adolescence is less likely and delayed school progression may merely be considered an indicator of risk for mental health problems.

Keywords: Adolescence, confounding, delayed school progression, general mental health and SDQ

INTRODUCTION

Mental health difficulties are both common and debilitating in childhood. About one-third of all children experience mental health problems that affect everyday functioning^{1,2}. Without adequate treatment these symptoms often persist into adulthood³. Since approximately fifty percent of all lifetime mental disorders arise in the mid-teens⁴, recent attention has focused on early detection and intervention during adolescence.

Several studies show that poor cognitive function or intellectual achievement is present before the onset of several mental disorders. Low intelligence coefficient (IQ) has predominantly been associated with later development of schizophrenia⁵. Similar associations have been found for other psychiatric illnesses such as severe depression⁶ and anxiety disorders⁷. Indeed, some studies suggest that pre-morbid low intellectual functioning is related to overall risk of psychiatric disorders in adulthood^{8,9}. Various mechanisms have been suggested to underlie this relationship, including the hypothesis that impairments in IQ or other cognitive functioning reflect neurodevelopmental changes which may predispose to psychiatric disorders^{10,11}. Several studies have demonstrated associations between poor scholastic achievement and mental disorders during adolescence or adulthood¹²⁻¹⁵. Repeating a grade is previously used as an indicator of scholastic underachievement and is for instance related to the risk of schizophrenia and other psychoses¹⁴. However, few studies investigated poor school achievement as an independent risk factor for the development of mental health problems during adolescence¹³. We therefore studied the association between a delay in school progression and mental health problems in adolescents, and adjusted for potential confounders.

METHOD

We conducted a cross-sectional population-based study of adolescents attending secondary schools in The Netherlands. The study population was an unselected sample of 10,803 adolescents at secondary school (age 12-18) who were routinely surveyed by the Community Health Service Central Netherlands & Eemland (GGD). Dutch secondary school has four main levels of education that prepare for further education. For the purpose of this study we divided the group in those who were preparing for polytechnic or academic training and those that were focussing on vocational training.

The survey took place during autumn 2007 and was conducted alongside prevention programs in all secondary schools in the in the province of Utrecht, excluding the City of Utrecht. The region includes both urban and rural areas; about 34% of the study population lives in an urban area. Participation was determined at school level and 45 schools (71% of the schools invited) participated. The most common reasons for schools not to participate were lack of time, change in management, or participation in other research projects. 84% of all students in the participating schools completed the questionnaire, non-response was mostly due to absence because of illness or truancy. Institutional Review Board approval was not required for this study since it was an anonymous questionnaire obtained for public health purposes.

Measurements

All students were asked to complete an anonymous digital questionnaire in the classroom.

Mental health problems

Mental health problems were defined as a score in the clinical range of the Dutch translation of the self-reported Strengths and Difficulties Questionnaire (SDQ)¹⁶. The Dutch translation of the self-reported SDQ is validated¹⁷. The SDQ has a specificity of 94.6% (95% CI 94.1-95.1) and a sensitivity of 63.3% (95% CI 59.7-66.9) to identify adolescents with a psychiatric disorder¹⁸. The SDQ consists of 25 items on psychosocial attributes. Each item is scored on a 3-point scale with 'not true', 'somewhat true', and 'certainly true'. These 25 items are divided into 5 subscales, each with 5 items: emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems, and pro-social behaviour. The summed score, excluding the items about pro-social behaviour, generates a total difficulties score, with a range of 0 to 40. The SDQ total difficulties score can be divided into normal (0-15), borderline (16-19) and clinical scores (20-40)¹⁶. To identify those with clinically relevant symptoms, the outcome was dichotomized into normal to borderline and clinical.

Poor school achievement

We used delayed school progression as marker of previous poor school achievement. A student was considered a poor school achiever when his age was at least 1.5 years above the mean age for his grade. This stringent cut-off allowed us to identify adolescents who had failed to progress as expected to the next grade on at least one occasion at any stage of primary or secondary school¹⁹.

Potential confounders

Potential confounders were determined based on the literature and availability in the school survey that assessed poor school achievement and mental health problems. Potential confounding factors were categorized into six different subgroups: socio-demographic factors, adverse life events, school-related factors, risk taking behaviour, health & lifestyle and miscellaneous factors. The content of the questionnaires can be found in the appendix.

Socio-demographic factors

Several socio-demographic factors were measured: gender, age (defined as low: under 14 years old), immigrant status, marital status of parents and socio-economic position²⁰ and urbanization²¹.

Adverse life events

The following adverse life events were assessed using adolescents' self-report: death of a first degree relative or another loved person, chronic disease or long lasting hospitalization of the adolescent himself or a first degree relative, parental alcohol problem or addiction, psychiatric disease in a first degree relative, parental divorce, domestic violence (between parents or victimizing the adolescent), molestation by someone other than the parent and sexual abuse²⁰.

School-related variables

The following school-related variables were measured: educational level at secondary school¹³, bullying, victimization²², school perception²³, truancy²⁴, perceived school safety²⁵, getting along with classmates and having close friends in school.

Risk taking behaviour

Substance use was assessed by questions about frequency of consumption of alcohol, tobacco, marijuana, other illicit drugs and addiction^{26,27}. Sexual risk taking behaviour was measured by condom use, lifetime multiple sexual partners and a history of sexually transmitted diseases (STDs).

Health and lifestyle

Healthy lifestyle was measured by seven variables: physical exercise, regular breakfast²⁸, fruit and vegetable consumption, overweight (BMI according to age), weight perception, excessive television/computer usage, absence at school due to illness and use of painkillers.

Miscellaneous factors

Family care, future perspective on life and parental involvement.

Data analyses

Missing data

The SDQ was complete for 11,291 adolescents (247 incomplete cases (2.1%) were excluded). Also, data were missing for multiple sexual partners (477 missing cases (4.2%). Because of the relatively small amount of missing data casewise exclusion of missing cases was performed. Furthermore, outliers with age older than 20 were excluded (N=10) as was one outlier with total SDQ score above 36. In total, data from 10,803 cases were analyzed.

Statistical analysis

All data were analysed using SPSS 19.0 for Windows. Bivariate non-parametric correlations were performed to identify multicollinearity between different variables (Kendall's $\tau > 0.8$)²⁹. As described above, potential confounders were selected based on literature. We used the large set of potential risk factors to perform a data-driven approach. Therefore, we divided the analysis in three different phases. First, we analyzed the crude unadjusted association between delayed school progression and current mental health problems. The crude odds ratio (OR) with 95% confidence interval (CI) was determined using logistic regression analysis. Secondly, covariates were tested as to whether they (1) were significantly correlated with both poor school achievement and mental health problems, and (2) altered the association between delayed school progression and mental health problems by at least ten percent³⁰. The final step in the analysis was the composition of a predictive model using multivariate logistic regression adjusting for only the confounding factors that were obtained in step two of the analysis. Significance level was set as $p = 0.05$.

RESULTS

The sample consisted of 10,803 participants, 99% of the participants were between 12 and 18 years old (range: 10 – 19 years), with a mean age of 14.2 (SD = 1.6) and 49.8% male. Gender was equally distributed. Most participants were Dutch and living with both parents. 35.4 % Of the pupils were identified as delayed in their school progression. Male gender (OR 1.40, 95% CI 1.15 – 1.69) was associated with delayed school progression. Adolescents with a non-Dutch ethnicity had higher odds for a delay in school progression (OR 2.77, OR 95% CI 2.27 – 3.73). Mental health problems, however, were equally distributed by age, gender and ethnicity.

Table 1. The distribution of different demographic variables in the full sample, the clinical °SDQ group and their association with clinical SDQ.

Variables	Full Sample N (%)	Clinical SDQ N (%)	Association SDQ OR (95% CI)
Male gender	5378 (49.8)	260 (53.3)	1.16 (0.97-1.39)
Age (mean, range)	14.17 (10-19)	14.19 (10-18)	1.01 (0.95-1.07)
Non-Dutch ethnicity	2091 (19.4)	93(19.1)	0.98 (0.78-1.24)
Not living with both parents	2390 (22.1)	150 (30.7)	1.60 (1.31-1.95)*
Low SES [^]	929 (8.6)	95 (19.5)	2.75 (2.17-3.48)*
Vocational level of education (missing 148)	5538 (52.0)	327 (68.1)	2.04 (1.67-2.48)*
Urbanization (missing 1491)			
• Less than 1000 (ref.)	3314 (35.6)	146 (36.9)	...
• 1000 - 1499	4054 (43.5)	166 (41.9)	0.93 (0.74-1.16)
• 1500 - 2499	1859 (20.0)	81 (20.5)	0.99 (0.75-1.31)
• 2500 or more	85 (.9)	3 (.8)	0.79 (0.25-2.54)

* *significant associations at $p < 0.05$*

° SDQ: Strengths and Difficulties Questionnaire

[^]SES: SocioEconomic Status

Bivariate analysis did not show multicollinearity between different variables. Table 1 shows the demographic characteristics of this population; information about other variables is added to the appendix in a supplementary table. Both of these tables show the distribution of variables analysed in the whole sample and clinical SDQ group, plus their relation with mental health problems. Analysis of potential confounders yielded a subgroup of variables which were added to the logistic models. (We selected only those confounders that were correlated with delayed school progression and SDQ and altered the association between delayed school progression and SDQ). These covariates were mainly adverse life events: sexual abuse, domestic violence and parental problems with alcohol or addiction. Other confounders were perceived problems with money or income and irregular breakfast. Since many control variables were related to age, gender and ethnicity, these factors were also included in the prediction model. Table 2 shows both the unadjusted and the adjusted prediction model. The unadjusted model consists of the crude association between delayed school progression and mental health problems (OR 1.83, 95% CI 1.27-2.62). In the adjusted model all the potential confounding factors were entered together. In the adjusted logistic regression model the association between delayed school progression and clinical SDQ was not statistically significant (OR 1.38, 95% CI 0.91-2.10). Since the association was not longer significant, analysis of factors that might also act as mediating factors was redundant.

Table 2. Prediction models showing delayed school progression as a predictor for mental health problems.

Predictor	<i>Unadjusted model</i>	<i>Adjusted model</i>
	Odds Ratio (95% CI)	<i>confounders</i> Odds Ratio (95% CI)
Delayed school progression	1.83 (1.27 - 2.63)*	1.38 (0.91 – 2.10)*
Socio-demographic factors:		0.91 (0.85-0.97)*
Low age		1.34 (1.11-1.63)*
Male gender		0.69 (0.54-0.89)*
Dutch ethnicity		
Economic problems		3.58 (2.85-4.51)*
Irregular breakfast		2.09 (1.68-2.61)*
Adverse life events:		
Sexual abuse		1.92 (1.32-2.80)*
Molestation by parents		2.10 (1.43-3.08)*
Violence between parents		1.55 (1.06-2.27)*
Parental problems with alcohol / addiction		1.90 (1.37-2.64)*

* *significant associations at $p < 0.05$*

DISCUSSION

In this cross-sectional study we investigated the association between scholastic achievement and current mental health problems in adolescents. We demonstrated that delayed school progression, used as a proxy for poor school achievement, was associated with adolescent mental health problems. After adjusting for potential confounding factors the association was no longer significant. These findings indicate a possible role for delayed school progression as a risk marker for mental health problems at adolescence, but did not provide evidence that delayed school progression is a causal risk factor for mental health problems. However this does not rule out the possibility that school performance may be associated with specific psychiatric outcomes such as schizophrenia. The factors that we identified as confounders are important to consider in further studies.

Strengths and limitations

The main strengths of this study were the large population-based sample with adolescents of both genders and the richness of the data, particularly on potential confounders. Furthermore, a delay in school progression is an objective measure and not subject to recall bias. The response rate was generally good. Moreover, the association between delayed school progression and mental health problems might have been stronger when non-responders would have joined the study since truants or frequently ill students are probably more likely to have high SDQ scores and problems with scholastic achievement.

This study also has limitations. Delay in school progression was a rather crude proxy for poor school performance and children with delayed school progression probably constituted a heterogeneous group, since the delay could have been the result of enrolling in primary school at a relatively old age or language problems. We reduced this problem considerably by adjusting for covariates, such as ethnicity, and by picking a stringent cut-off point for delayed school progression to include only children with a definite history of scholastic underperformance. Another limitation was the self-reported SDQ as an outcome measure. Although validated and used widely as a measure for mental health problems, complementary information from teachers and parents would improve the sensitivity and specificity. Furthermore, the prevalence of mental health problems in our study population was low compared with international studies using the SDQ¹⁸. Dutch children have a tendency to score lower on the SDQ than UK children; about 6% of all Dutch children score above the UK cut-off point² and in our sample 4.5% of the participants scored in the clinical range. Additionally, the included children were aged between 10 and 19 years old (99% between 12 and 18 years) and mental health problems may differ between the younger and older participants. This study was also limited by its cross-sectional design. Delay in school progression and mental health problems were measured at the same moment, thus we cannot rule out that mental health problems could have preceded the delay in school progression earlier in youth. However, previous prospective studies on educational performance showed that poor educational attainment often predicts development of psychiatric disorders¹²⁻¹⁵.

These measures may be more related to intellectual functioning than a delay in school progression because the latter is more affected by other aspects such as social and emotional development during school-age. Thus, further research is needed to examine the potential role of school performance as an intermediate factor for different risk factors of mental health problems and longitudinal effects of poor school performance.

Interpretation of findings

Contrary to most previous studies addressing poor educational achievement and psychiatric problems, we found no association after adjusting for confounders. This finding is in contrast to previous studies that have shown associations between poor school performance and later psychosis. It is possible that the adolescent age is too early to detect the effects of neurobiological changes on mental health. Furthermore, we focused on general mental health problems, instead of the development of specific (mainly psychotic) disorders in the majority of previous studies.

In addition, poor school achievement can be seen as an event that might mediate the impact of other risk factors for mental health problems. Thus, poor school achievement might function as a trigger for alterations in the causal pathway of genetic and environmental factors underlying neurobiological changes leading to mental disorders.

Lastly, most studies used other measures of poor school performance, like school level¹³, literacy skills¹² and school grades^{14,15}. These measures may be more related to intellectual functioning than a delay in school progression because the latter is more affected by other aspects such as social and emotional development during school-age. Thus, further research is needed to examine the potential role of school performance as an intermediate factor for different risk factors of mental health problems and longitudinal effects of poor school performance.

CONCLUSION

Overall our results showed that delayed school progression is a risk marker of mental health problems in school-aged children, but that this association is largely explained by confounding. This is consistent with the view that poor school performance is a risk indicator for particular psychiatric disorders but not for general mental health problems in adolescents.

Acknowledgements: We are grateful to the employees of the Municipal Health Service Central Netherlands for collection of the data.

Additional file: Detailed content of the questionnaire and Supplementary table: distribution of all variables in the sample, clinical SDQ group and their association with SDQ.

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Appendix to “Delayed school progression and mental health problems in adolescence: a population-based study in 10,803 adolescents.”

Wanda Tempelaar, Christiaan Otjes, Clothilde Bun, Carolien Plevier, Willemijn van Gastel, James MacCabe, René Kahn, Marco Boks

Details of the full assessment by domain:

Socio-demographic factors

Immigrant status: ‘both parents Dutch’ or ‘one or both parents born abroad’.

Marital status parents: ‘living with both parents’ or ‘other’.

Socioeconomic position: ‘no, parents never experienced problems with money and/or income’ or ‘yes, experienced or experiencing right now’.

Urbanization: measured in four levels of urbanization according to the Dutch Central Bureau of Statistics³¹.

Adverse life events

All adverse life event factors were answered on a 2-point scale: ‘Yes experienced or experiencing now’ or ‘no, never experienced’.

School-related factors

Educational level at secondary school: ‘vocational training’ or ‘polytechnic or academic training’.

Bullying: participated in bullying of other student in the last three months: ‘yes’ or ‘no’

Victimized: was victim of bullying during in the last three months: ‘yes’ or ‘no’

School perception, dichotomized in: ‘(very) nice’ or ‘okay, not nice and terrible’

Truancy: more than 3 hours last 4 weeks: ‘yes’ or ‘no’.

Getting along with classmates, dichotomized in: ‘almost none’ or ‘almost all, more than half and some’.

Good friends in school, dichotomized in: ‘no good friends’ or ‘one, some and many good friend’

Feeling unsafe at school, dichotomized in: ‘never or sometimes’ or ‘(very) often’

Risk taking behaviour

Alcohol: weekly alcohol usage: ‘yes’ or ‘no’

Tobacco: daily smoking: ‘yes’ or ‘no’

Marijuana: marijuana consumption last month: ‘yes’ or ‘no’

Hard drugs: hard drugs consumption last month: ‘yes’ or ‘no’

Perceived difficulties with alcohol or addiction ever or perceives difficulties right now: ‘yes’ or ‘no’

Condom usage: used a condom during last sexual intercourse: ‘yes’ or ‘no’

Multiple sexual partners: four or more different sexual partners lifetime: ‘yes’ or ‘no’

Having a history of sexually transmitted disease (STD): ‘yes’ or ‘no’

Health and lifestyle factors

Physical exercise according to movement standard as defined by Dutch guideline healthy movement³²: 'yes' or 'no'.

Regular breakfast (at least six days a week): 'yes' or 'no'.

Fruit consumption as defined by Dutch health standard³³: 'yes' or 'no'.

Daily vegetables consumption: 'yes' or 'no'.

Weight perception: 'way too thin', 'bit thin', 'normal', 'bit thick', 'way too thick'.

Excessive television usage: more than two hours a day or more: 'yes' or 'no'.

Excessive pc usage: more than two hours a day or more: 'yes' or 'no'.

Absence at school due to illness: at least one day or more last four weeks: 'yes' or 'no'.

Frequent pain killer use: more than one every week in the past month: 'yes' or 'no'.

Miscellaneous factors

Future perspective: the upcoming five year will be: '(very) good - not good, not bad' or '(very) bad'.

Family care: one or more of the following: 'care for brothers and sisters; like dressing, feeding, bringing to school and babysitting' or 'taking care of things; like going to pharmacy, coming to doctor/hospital or translating' or 'emotional support giving to sick parent or family member; like talking, listening and providing comfort'.

Parental involvement is measured in two ways: (1) Often joining parent teachers meetings (PTM), dichotomized in: '(almost) always' or 'sometimes and (almost) never' and (2) parental help with homework both dichotomized in: 'yes' or 'no'.

For the supplementary table: all variables were analysed on full sample size unless otherwise denoted in the first column. In case of smaller sample size, the number of missing values in the clinical SDQ group can be found in the left column directly after the sample size.

References Appendix

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Supplementary table: Distribution of all variables in the sample, clinical SDQ group and their association with SDQ.

Variables	Full Sample N= 10,803 N (%)	Clinical SDQ N= 488 N (%)	Association SDQ OR (95% CI)
Family care task	748 (6.9)	80 (16.4)	2.83 (2.20-3.64)*
Poor future perspective (N = 10779; 486)	191 (1.8)	83 (17.1)	19.42 (14.35-26.30)*
Poor parent involvement			
• Homework (N = 10802; 0)	632 (5.9)	83 (17.0)	3.65 (2.84-4.69)*
• PTM (N = 10802; 0)	3030 (28.1)	192 (39.3)	1.71 (1.42-2.06)*
Loss of a relative	7389 (68.4)	352 (72.1)	1.21 (0.99-1.48)
Chronic disease / long hospitalization self	1893 (17.5)	130 (26.6)	1.76 (1.43-2.17)*
Chronic disease / long hospitalization relative or loved person	4303 (39.8)	245 (50.2)	1.56 (1.30-1.87)*
Parental addiction	467 (4.3)	68 (13.9)	4.02 (3.06-5.30)*
Psychiatric disease in one or both parents	636 (5.9)	77 (15.8)	3.27 (2.53-4.23)*
Psychiatric disease in brother or sister	550 (5.1)	56 (11.5)	2.58 (1.92-3.45)*
Parental divorce	2038 (18.9)	134 (27.5)	1.67 (1.36-2.05)*
Domestic violence between parents	380 (3.5)	57 (11.7)	4.09 (3.04-5.51)*
Molestation by parent(s)	331 (3.1)	58 (11.9)	4.96 (3.68-6.69)*
Molestation by other adult	244 (2.3)	44 (9.0)	5.01 (3.57-7.04)*
Sexual abuse	356 (3.3)	53 (10.9)	4.03 (2.96-5.47)*
Bullying (N = 10802; 0)	2987 (27.7)	240 (49.2)	2.67 (2.22-3.20)*
Victimized (N = 10802; 0)	1961 (18.2)	222 (45.5)	4.12 (3.42-4.95)*
Poor school perception	4566 (42.3)	345 (71.1)	3.56 (2.91-4.34)*
Frequent truancy	753 (7.0)	108 (22.1)	4.26 (3.39-5.35)*
Feeling unsafe at school (N = 10802; 0)	246 (2.3)	74 (15.2)	10.54 (7.89-14.08)*
Not getting along with classmates (N = 10802)	158 (1.5)	48 (9.8)	10.12 (7.12-14.39)*
No good friends in school (N =10802; 0)	130 (1.2)	29 (5.9)	6.39 (4.18-9.76)*
Weekly alcohol use	1933 (17.9)	168 (34.4)	2.54 (2.10-3.09)*
Marijuana use last month	676 (6.3)	96 (19.7)	4.11 (3.24-5.22)*
Daily smoking	786 (7.3)	701 (6.8)	2.89 (2.26-3.70)*
Drinking problem/addiction	338 (3.1)	268 (2.6)	6.28 (4.74-8.31)*
Hard drug use last month	129 (1.2)	88 (.9)	10.66 (7.27-15.63)*
Condom used last sexual intercourse (N=1743; 173)	566 (32.5)	484 (30.8)	2.02 (1.47-2.78)*
Multiple sexual partners lifetime	393 (3.6)	329 (3.2)	4.52 (3.45-6.09)*
History of STD	77 (.7)	54 (.5)	9.40 (5.72-15.45)*
Insufficient physical exercise	1529 (14.2)	99 (20.3)	1.58 (1.26-1.99)*
Insufficient fruit consumption	2235 (20.7)	102 (20.9)	1.01 (0.81-1.27)
Insufficient vegetables consumption	6932 (64.2)	322 (66.0)	1.09 (0.90-1.32)
Non-regular breakfast	1626 (15.1)	145 (29.7)	2.52 (2.06-3.09)*
Overweight (N = 10605; 479)	839 (7.9)	55 (11.5)	1.55 (1.16-2.07)*
Perception of overweight (N = 10802; 0)	3133 (29.0)	219 (44.9)	2.07 (1.72-2.48)*
Excessive computer usage	987 (9.1)	166 (34.0)	2.39 (1.99-2.87)*
Excessive television usage	3082 (28.5)	217 (44.5)	2.08 (1.73-2.50)*
Frequent painkiller usage (N = 10802; 0)	887 (8.2)	109 (22.3)	3.53 (2.81-4.42)*
School absence due to illness	3802 (35.2)	3553 (34.4)	1.98 (1.65-2.38)*

 * significant associations at $p < 0.05$

Chapter 2

3

Educational level, underachievement and general mental health problems in 10,866 adolescents

Wanda M. Tempelaar MD, Nelleke de Vos MSc, Carolien M. Plevier MSc,
Willemijn A. van Gastel PhD, Fabian Termorshuizen PhD, James H.
MacCabe MD PhD, Marco P.M. Boks MD PhD

ABSTRACT

Objective: Previous research suggests that cognitive functioning is associated with the risk of several adult psychiatric disorders. This study investigates whether adolescents who perform worse than expected at secondary school are at a higher risk for general mental health problems.

Method: In a cross-sectional survey comprising 10,866 Dutch adolescents aged 13-16 years, underachievement at secondary school was defined as the discrepancy between predicted school grade and actual grade one or three years later. Mental health problems were assessed with the Strengths and Difficulties Questionnaire (SDQ). We investigated the association of underachievement with mental health problems using logistic regression, adjusting for potential confounders.

Results: Underachievement was associated with general psychopathology in pupils aged 13-14 (OR: 1.86, 95% CI 1.47-2.37) and in pupils aged 15-16 (OR: 2.05, 95% CI 1.67-2.52) in a multivariate analysis including sociodemographic factors. The association between underachievement and mental health problems was attenuated when school factors such as teacher advice and interaction between underachievement and teacher advice were added, but underachievement remained significantly associated with mental health problems in adolescents in the higher educational tracks (pupils aged 13-14 OR: 2.22, 95% CI 1.07-4.60 and OR: 2.41, 95% CI 1.10-5.30, age 15-16 OR 2.63, 95% CI 1.38-5.03). This association was most pronounced for the hyperactivity subscale of the SDQ.

Conclusions: Underachievement at secondary school is associated with general mental health problems, especially with hyperactivity symptoms, in pupils who started at high educational tracks.

What's New: Whereas a higher risk for mental disorders in adolescents with poor educational performance is well established, we focus on the reciprocal relationship by showing that underachievement acts as an indicator of common mental health problems, and does so more strongly for adolescents initially placed into higher education tracks than for those placed into lower or medium level educational tracks.

Keywords: Adolescence, underachievement, school-performance, general mental health problems

INTRODUCTION

Adolescence is a highly important phase in the aetiology of psychiatric disorders. Incidence rates of mental health problems show a marked increase during this period of the life course and studies show that many adult mental disorders commence with early symptoms during childhood or adolescence¹⁻³. Cognitive development is central to the changes that occur during adolescence⁴. It is well known from previous studies that abnormalities in cognitive development often precede the development of severe mental disorders^{5,6}. Such cognitive deficits can be detected during adolescence using cognitive tests or scholastic performance⁷. For instance studies of premorbid low intelligence^{8,9}, poor school performance^{7,10,11} and a decline in cognitive functioning^{12,13} show a relationship with the development of schizophrenia. Severe depression and anxiety disorder are also associated with cognitive deficits^{14,15}.

Several studies show associations between poor scholastic achievement and mental disorders during adolescence or adulthood¹⁶⁻²¹. A systematic review by Esch et al reported on the bidirectional associations between psychopathology and school dropout. Externalizing disorders and substance use disorders were strongly related to school dropout, especially when the disorders developed at early age^{20,21}. It seemed that internalizing disorders such as depression did not have a direct effect on early school leaving, but occurred after school dropout²⁰. Breslau et al reported that mental disorders were significantly related to early termination of education and showed that 10% of high school termination was attributable to mental disorders¹⁷. Furthermore, educational problems and specifically lower grade point average (GPA) are associated with depression in adolescents^{18,19}. Several studies have shown that Attention-deficit/hyperactivity disorder (ADHD) is associated with poorer educational outcomes, for instance poor grades, poor reading and math standardized test scores, increased grade retention and relatively low rates of high school graduation^{22,23}. Less is known about the relationship between cognitive performance and common mental health disorders in adolescence. It remains unclear whether a decline in scholastic or cognitive performance is related exclusively to certain disorders, or also to common mental health problems in the population. We therefore investigated the relationship between common mental health problems and a broad measure of cognitive performance in a large adolescent population at secondary school. We used

educational level as a proxy for general intellectual functioning, and underachievement at secondary school, compared to predicted grades, as a proxy for decline in cognitive performance. We hypothesized that a decline in cognitive performance would be associated with general mental health problems.

METHOD

Study population

The community health services in the Netherlands conduct regular cross-sectional surveys at secondary schools to investigate general wellbeing of adolescents²⁴. In the area of the Utrecht province, secondary schools are invited to cooperate every four years. The schools are located in a region that contains both urban and rural areas; approximately 34% of the participants live in an urban area. Sociodemographic characteristics were compared with a large national cohort study in Dutch adolescents at secondary schools²⁵. The current cross-sectional population-based sample is obtained in the 2011-2012 wave of this ongoing survey. In the beginning of the 2011-2012 school year, 63 schools were invited to take part in this research project and ultimately 41 schools agreed to participate. The reasons for schools not to participate included busy schedules and involvement in other research projects. Adolescents in the second year (age 13-14) and fourth year (age 15-16) at secondary school and their parents were asked to participate in an opt-out procedure. Over 99% of the approached adolescents consented. Pupils who agreed to participate filled in a digital, anonymous questionnaire in the classroom. This assessment included questions about psychosocial functioning, lifestyle, health, stressful events and school-related factors. The average response of the pupils at school was 77%, non-response mostly due to absence of pupils because of illness or truancy, and at one school an IT failure prevented some pupils from filling in the questionnaires. The total sample included 10,803 adolescents.

Measurements

Underachievement

The Dutch education system consists of eight years of primary education, four to six years of secondary education and two to six years of higher education. Education is compulsory until the age of 16 in the Netherlands (figure 1) and state schools provide almost all primary and secondary education. In primary school (age 4-12), all children are educated at the same level. In secondary school (starting at age 12), children can attend four different tracks of

education (apart from special education): low, medium and high prevocational and pre-university education²⁶. These tracks are associated with general intelligence: the mean IQ among pupils in the low prevocational track is 92.0 (SD 11.7), medium prevocational: 98.1 (SD 9.2), high prevocational track: 106.9 (SD 10.6) and preparatory university: 115.6 (SD 11.8)²⁷. At the end of primary school, all pupils take a standardized national exam to test their aptitude at age 11-12 years. Their primary school teacher refers them to their starting track (low, medium, high prevocational or pre-university) at secondary school based on their results on the exam and the child's entire primary school record²⁶. Some teachers recommend a pupil to two alternative tracks at once, to provide the opportunity for pupils to experience both tracks when there is doubt about the appropriate educational level. These pupils are then taught in a 'combination class' in which students from two adjacent tracks are grouped together. During their school career all pupils can either downgrade or upgrade according to their actual performance at school. At the end of secondary school, all pupils take national state exams at their respective level and can enter further education in the three follow-up tracks: vocational education (54% of all pupils), polytechnics (28% of all pupils) or university (18% of all pupils)²⁸.

Scholastic underachievement is generally described as lower scholastic performance than expected²⁹. This expectation can be based on various previous measurements, for example prior attainment or aptitude tests³⁰. In our study, underachievement was defined as a downgrade in the pupil's educational track, for example: a student started secondary school in the medium track, but attended the low track in the second or fourth year. This decline in educational track was classified as underachievement. Pupils who were recommended to two consecutive tracks, were only defined as underachievers when they attended an entire track below that recommended by their teachers.

Mental Health

Psychosocial functioning was measured with the Strengths and Difficulties Questionnaire (SDQ)³¹. The SDQ is a brief screening questionnaire that focuses on common forms of psychopathology in adolescents aged 11 to 16 years. The SDQ has a specificity of 94.6% (95% CI 94.1-95.1) and a sensitivity of 63.3% (95% CI 59.7-66.9) to identify adolescents with a psychiatric disorder³². The Dutch translation of the self-reported SDQ has been validated³³. The SDQ consists of 25 items on psychological attributes, scoring on a 3-point Likert

scale (not true/somewhat true/certainly true). The scale is subdivided into 5 scales of 5 items: emotional symptoms, conduct problems, hyperactivity / inattention, peer relationship problem and pro-social behaviour. The scores on all subscales but pro-social behaviour are summed to generate a total difficulties score (0-40). The self-reported total difficulties score can be divided in a normal (0 to 15), borderline (16 to 19) and clinical score (20 to 40). Scores in borderline and clinical range were taken together as deviant SDQ scores³¹. The Dutch translation of the self-reported SDQ is validated and the internal consistencies of the total difficulties score (Cronbach's alpha: 0.70) and three of the separate subscales were found to be reasonable (Cronbach's alpha: emotional symptoms scale: 0.63; hyperactivity-inattention: 0.66; prosocial behaviour: 0.60), the internal consistencies of the conduct problems (Cronbach's alpha: 0.47) and peer problems scale (Cronbach's alpha: 0.39) were below acceptable limits³³.

Time line

Although the survey data is cross-sectional in nature, part of the data is historic, providing a temporal dimension to this study. The school advice by the teacher of the primary school take place in the last year of primary school. The downgrading takes place between the date of advice, and the second respectively fourth year of secondary school (Figure 2 in appendix).

Socio-demographic factors

Information on age (in years), gender, ethnicity, household composition and family affluence was collected in the self-report questionnaire. We categorized ethnicity as native or non-native based on the country of birth of the parents. Participants were considered non-native when one or more parents were born abroad. Household composition was divided into living with both biological parents versus one or none of them. Socio economic status was measured with the Family Affluence Scale (FAS), which is a validated measure of family wealth, developed for adolescent responders³⁴.

Data analysis

Missing data

There were 313 missing values (2.8%) for current educational track, 19 incomplete SDQ questionnaires (0.2%) and 2 missing values for grade (0.0%); listwise exclusion was applied. Since pupils with the lowest teacher advice could not be classified as underachievers, we excluded 1,641 (14.7%) cases from our analyses, resulting in 9,225 cases for analysis. Pupils were either in the second or the fourth year of secondary school. Analyses are reported separately by school year.

Statistical analyses

Analyses were carried out with the statistical package for the social sciences (SPSS 20.0 for Windows). First, baseline characteristics were summarised using descriptive statistics. Bivariate non-parametric correlations between independent variables were performed to investigate potential multicollinearity (Kendall's $\tau > 0.8$). To examine whether underachievement was related to general mental health we used logistic regression analyses yielding odds ratios (OR) with 95% confidence intervals (95% CI). We then conducted a multivariate analysis in which sociodemographic variables were added to the model. Finally, we analysed a multivariate model containing all covariates, teacher advice dummy variables, and the interaction term of underachievement and teacher advice. Teacher advice was categorized according to the different tracks (including combination class). Post-hoc, we entered school as a random factor to provide for multilevel analysis for the 41 schools and analysed the association between underachievement and the three valid subscales of the SDQ.

RESULTS

The baseline characteristics of the participants are presented in table 1. The sample comprised 5,784 pupils in second and 5,082 in fourth school year. Mean age was 13.3 in year 2 with 68.2% of the pupils aged 13 and 27.7% aged 14. Mean age was 15.5 in year 4 with 55.9% of the pupils aged 15 and 36.1 aged 16 years. Gender was equally distributed. Most participants were Dutch, of high affluence and living with both parents. Compared with pupils in a large national population sample survey (WHO-Health Behaviour in School-aged Children: HBSC, 2009), our study sample was comparable regarding gender (50.6% female in our study versus 49% in HBSC), ethnicity (83.4% Dutch ethnicity versus 80% in HBSC) and household composition (83.3% were living with both parents versus 79.8% in HBSC) (Table 1)²⁵. Our study sample contained relatively less lower educated pupils: pupils in low prevocational level: 15.4% in our study sample versus 20% in HBSC, intermediate prevocational level: 26.9% versus 33%, high prevocational level 33.2% versus 23% and pre-university level 24.5% versus 24% (Table 1)²⁵. Furthermore, fewer adolescents were living in large cities and fewer pupils were living in families of low affluence: 2.1% of pupils were in low socio-economic class, 22.7% in middle and 75.2% in high, whereas in a large general population study 4.5% of pupils classified in low, 31.1% in middle and 64.4% in high socio-economic class²⁵. Table 1 shows 566 pupils classified as underachievers at age 13-14 (21.2% started in medium level, 9.9% in medium/ high, 29.2% in high, 21.9% in high/pre-university and 17.8% in pre-university level).

Table 1. Characteristics of study population

		Age 13-14		Age 15-16	
Full sample	N	5784		5082	
		Mean	s.d.	Mean	s.d.
Age		13.3	0.55	15.46	0.65
		N	%	N	%
Gender	Female	2918	50.4	2569	50.6
	Male	2866	49.6	2513	49.4
Ethnicity	Dutch	4819	83.3	4236	83.4
	Surinamese, Caribbean	110	1.9	129	2.6
	Turkish	100	1.7	66	1.3
	Moroccan	161	2.8	115	2.3
	Other	594	10.3	536	10.5
Family Affluence Scale	Low	119	2.1	110	2.2
	Middle	1246	21.5	1221	24
	High	4419	76.4	3751	73.8
Household composition	Lives with both parents	4888	84.5	4235	83.3
	Lives separated from one or both parents	896	15.5	844	16.6
	missing	0		3	0.1
SDQ	Normal	5066	87.6	4378	86.1
	Borderline	467	8.1	450	8.9
	Clinical	251	4.3	254	5
Teacher advise	Low (1)	843	14.6	798	15.7
	Medium (2)	731	12.6	642	12.6
	Medium / high (2/3)	971	16.8	883	17.4
	High (3)	793	13.7	640	12.6
	High / pre-university (3/4)	1359	23.5	1213	23.9
	Pre-university (4)	1087	18.8	906	17.8
Underachievement	No underachievement	5218	90.2	4309	84.8
	Underachievement	566	9.8	773	15.2

Table 2. Associations with deviant SDQ (odds ratio, 95% confidence intervals CI)

Predictor	Age 13-14		Age 15-16	
	OR	95 % CI	OR	95 % CI
Univariate analysis				
Underachievement	1.98	1.57-2.50**	2.08	1.70-2.55**
Multivariate analysis (1)				
Underachievement	1.86	1.47-2.37**	2.05	1.67-2.52**
Female gender	1.03	0.86-1.23	1.31	1.09-1.56*
Non-Dutch ethnicity	0.92	0.71-1.17	1.28	1.02-1.62*
Low affluence	1.29	0.72-2.33	1.85	1.09-3.12*
Separated from one or both parents	2.00	1.61-2.47**	1.23	0.98-1.55
Multivariate analysis (2)				
Underachievement	1.04	0.60-1.80	1.65	1.06-2.60*
Female gender	1.02	0.86-1.23	1.26	1.05-1.51*
Non-Dutch ethnicity	0.88	0.69-1.13	0.08	0.98-1.57
Low affluence	1.26	0.70-2.29	1.75	1.03-2.96*
Separated from one or both parents	1.96	1.58-2.43**	1.20	0.95-1.52
<i>Teacher advice *</i>				
Medium	Reference category		Reference category	
Medium / high	0.81	0.60-1.10	0.88	0.65-1.21
High	0.79	0.56-1.10	0.83	0.58-1.20
High / pre-university	0.61	0.45-0.82*	0.63	0.46-0.86*
Pre-university	0.48	0.35-0.67**	0.33	0.22-0.50**
<i>Underachievement * teacher advice #</i>				
Medium ⇒ Low	Reference category		Reference category	
Medium / high ⇒ Low	1.67	0.69-4.02	0.91	0.45-1.87
High ⇒ Medium	1.82	0.89-3.71	0.93	0.49-1.77
High / pre-university ⇒ Medium	2.22	1.07-4.60*	1.43	0.76-2.70
Pre-university ⇒ High	2.41	1.10-5.30*	2.63	1.38-5.03*

* reference category: teacher advice medium prevocational

reference category: teacher advice medium prevocational, downgraded to low prevocational

* significant at $p < .05$, ** significant at $p < .001$

There were 773 underachievers at age 15-16 (19.1% started in medium level, 11.6% in medium/ high, 24.2% in high, 18.5% in high/ pre-university and 26.5% in pre-university level). Most underachievers downgraded one track; 77.2% of the underachievers at age 13-14 and 73.0% of the underachievers at age 15-16 attended exactly one track below that recommended by their teachers. The proportion of downgrading in our sample was 10% after two years and 15% in four years (Table 1), this is comparable with results in a national cohort study of school progression at secondary school: 12% of the pupils downgraded in five years to a lower educational track than they had started in the beginning of secondary school³⁵. Over 85% of the pupils scored in the normal range of the SDQ in both age groups (Table 1). The mean SDQ score was low: mean score in age group 13-14 was 9.5 in boys and 9.7 in girls compared to mean SDQ score of 13.9 in boys and 13.4 in girls in HBSC study in 14-year old pupils in the Netherlands in 2009 (Table 1)²⁵. In the older age group our mean total score was also lower: 9.6 in boys and 10.4 in girls compared with 14.9 in 16-year old boys and 18.6 in 16-year old girls (Table 1)²⁵. These contrasts are probably due to differences in the sociodemographic characteristics of this population sample since the pupils in our sample were predominantly of middle/high social economic class and Dutch nationality. Table 2 presents the results of our analyses. The univariate and multivariate analysis after adjustment for socio-demographic variables of the association of mental health problems with underachievement showed that the odds for reaching the threshold of deviant SDQ score are increased for pupils with underachievement in both age groups (age 13-14: OR 1.98, 95% 1.57-2.50; OR 1.86, 95% 1.47-2.37 and age 15-16: OR 2.08, 95% 1.70-2.55; OR 2.05, 95% 1.67-2.52). In the multivariate analysis including teacher advice and the interaction between underachievement and teacher advice, underachievement was significantly related to psychopathology in the older age group (OR 1.65, 95% 1.06-2.60). A significant interaction effect between underachievement and teacher advice occurred in both age groups in the higher tracks (age 13-14 OR: 2.22, 95% CI 1.07-4.60 and OR: 2.41, 95% CI 1.10-5.30 and age 15-16 OR 2.63, 95% CI 1.38-5.03). In addition, teacher advice itself was significantly and inversely associated with psychosocial problems in the two highest tracks (age 13-14: OR: 0.61, 95% CI 0.45-0.82; OR: 0.48, 95% CI 0.35-0.67, age 15-16: OR: 0.63, 95% CI 0.46-0.86; OR: 0.33, 95% CI 0.22-0.50). Living separated from one or both parents was related to a deviant SDQ score in the younger age group, female gender and low affluence were related to a deviant SDQ score in the older age group (Table 2). Post-hoc analyses on the three valid subscales of the SDQ (significance level set at $p < 0.01$ to correct for multiple testing) showed that underachievement was significantly associated with

deviant scores on the hyperactivity subscale and not with the emotional problems or pro-social subscale (age 13-14: OR: 1.94, 95% CI 1.57-2.40, $p < 0.001$, Age 15-16: OR: 1.82, 95% CI 1.51-2.19, $p < 0.001$) (Appendix table 3). Gender differences between normal and deviant scores on SDQ subscale hyperactivity were not significant. We tested for an additional effect of separate schools in a mixed model analysis with underachievement, mental health problems and sociodemographic factors as indicators and school entered as a random factor to provide for multilevel analysis for the 41 schools. Results were not modified by this inclusion of school as random effect (results not shown). Furthermore, using an alternative cut-off of the SDQ such as computing the 15% highest scorers did not change the main results of our study.

DISCUSSION

In this large population-based cross-sectional study we investigated the relationship between scholastic performance and mental health in adolescents. First, we found evidence that underachievement at secondary school was associated with adolescent mental health problems. Second, we found that pupils with underachievement who started in higher tracks of education had larger odds for deviant SDQ scores than those who started out in medium tracks. Furthermore, post-hoc analysis showed that underachievement was particularly related to symptoms of hyperactivity. Our finding that downgrading in educational tracks at secondary school is associated with adolescent mental health problems is in line with previous research^{16-18,36}. Our results add to the existing evidence that not only school drop-out³⁶, lower results on educational tests^{7,17,19,22} and grade retention⁷ are related to psychopathology but also decline in educational track is included in this 'underachievement'. Furthermore, our results indicate different associations between mental health problems and underachievement at various tracks of education. Pupils who underachieved and started at a higher track, had higher odds for deviant SDQ scores, although pupils in higher educational tracks had lower risks of psychopathology compared with low educational tracks. This difference may be partially explained by the lower levels of psychosocial problems in higher tracks of education. The increase in psychosocial problems will therefore constitute a larger proportional increment in the higher levels compared to the lower levels.

This finding is in line with literature showing that pupils at low educational levels experience more deviant SDQ scores²⁵. Also, a significant amount of the variation in school performance at Dutch secondary schools and achievement is explained by intelligence^{27,37} and lower childhood IQ is related to an increased risk of several psychiatric disorders¹⁴. Another explanation for the difference found between pupils in higher and lower educational tracks might be that pupils in higher streams more often experience subclinical (or undiagnosed) ADHD symptoms. Bussing et al showed that graduation rates were lower for students with subthreshold ADHD than for students diagnosed with ADHD³⁸. Lastly, we showed that underachievement was particularly related to symptoms of hyperactivity. This is consistent with previous studies showing that the association with educational attainment is specific for various mental health disorders³⁶. Hyperactivity and attention problems especially predict negative academic outcomes after adjustment for IQ or prior school difficulties¹⁷.

Strengths and limitations

The main strengths of this study are the large population-based sample of adolescents. Participants were predominantly from Dutch origin, high affluence and living with both parents, which is representative of Dutch adolescents outside the large cities. We were able to investigate the effect of underachievement in different tracks next to the effect of other important variables such as sociodemographic factors. Furthermore, we looked at current mental health and both early and late underachievement, which gave us the opportunity to obtain a longitudinal perspective in a retrospective cross-sectional study.

This study should be viewed in the light of its limitations. First, this study is limited by its cross-sectional design. The association between low educational attainment and psychopathology is bidirectional; educational problems may both result from psychopathology or lead to psychopathology during childhood¹⁷. Several prospective studies have shown that psychiatric problems predict educational underachievement^{16,39} and also problems in educational attainment or cognitive deficits predict later development of psychiatric disorders^{11,14}. In our study, underachievement and mental health problems were measured at the same moment, thus we cannot rule out that mental health problems could have preceded scholastic underachievement. Second, scholastic underachievement is only measured in the time-span from the start of secondary until the second or fourth year at secondary school. This might be too short or too early to

adequately assess all underachievers. Furthermore, we caused a bias of higher socio economic class by not including the low level underachievers. Of note is that this study was conducted in an affluent western country and the results may not generalise to other populations. Fourth, in the multivariate analysis, we added information on important variables such as gender, ethnicity, affluence and household composition to adjust for potential confounding. Other, unmeasured confounding factors and residual confounding cannot be ruled out. A further limitation is that the self-reported SDQ is not as reliable in measuring psychosocial functioning as the multiple source version with information from parents and teachers. However, validity and reliability improve by administering the questionnaires in school classes and by assuring anonymity⁴⁰. Despite these limitations, the present study adds to the current discussion on cognitive development and psychopathology that a decline in scholastic achievement may be investigated as a marker for general psychosocial problems, especially in pupils who started at high track of education. Although this type of underachievement; downgrading in tracks, has not been investigated as much as educational test scores or school drop-out, it is very informative since it directly results in less education which may have life-long consequences for the affected individuals⁴¹. This adverse outcome emphasizes the need for early detection in adolescents to avoid development of severe mental health problems or educational attainment, which are both important for well-being during adulthood^{36,39,42}. Previous research showed that school personnel played an important role in both detection and the referral for help in childhood psychopathology⁴³. For instance systematic screening, school monitoring with training of teachers and other school personnel to identify children at risk and school-based health promotion programmes may be useful in daily practice of schools⁴⁴. It is then possible to investigate whether children in various tracks or types of education benefit differently from these interventions.

CONCLUSION

Underachievement at secondary school is associated with general mental health in pupils who started at a high educational level, especially with hyperactivity symptoms.

Acknowledgements

We are grateful to the employees of the Municipal Health Service Central Netherlands for collection of the data.

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Appendix

Figure 2. Time line

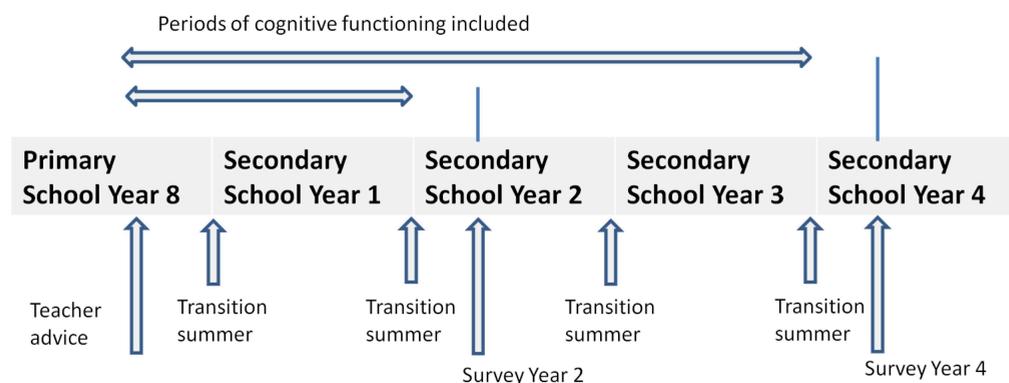


Table 3. Multivariate analyses valid sub scales SDQ (odds ratio, 95% confidence intervals CI)

Hyperactivity subscale

Predictor	Age 13-14		Age 15-16	
	OR	95 % CI	OR	95 % CI
Underachievement	1.94	1.57-2.40*	1.82	1.51-2.19*
Female gender	0.86	0.73-1.00	0.93	0.80-1.08
Non-Dutch ethnicity	0.69	0.55-0.86	0.90	0.72-1.12
Low affluence	0.79	0.42-1.46	1.03	0.58-1.81
Separated from one or both parents	1.58	1.30-1.92*	0.99	0.80-1.22
Teacher advise 1	1.22	0.95-1.57	1.01	0.78-1.31
Teacher advise 2	1.03	0.79-1.35	1.12	0.86-1.47
Teacher advise 3	0.92	0.72-1.17	1.08	0.85-1.38
Teacher advise 4	0.80	0.61-1.03	0.73	0.56-0.95

* significant at $p < .001$

* reference category: teacher advice medium prevocational

Emotional subscale

Predictor	Age 13-14		Age 15-16	
	OR	95 % CI	OR	95 % CI
Underachievement	1.37	1.01-1.85	1.40	1.09-1.82
Female gender	3.36	2.68-4.20*	4.52	3.57-5.73*
Non-Dutch ethnicity	0.74	0.55-1.00	0.87	0.66-1.16
Low affluence	0.84	0.54-2.16	1.20	0.63-2.31
Separated from one or both parents	1.42	1.10-1.83	1.24	0.96-1.61
Teacher advise 1	0.91	0.65-1.27	1.06	0.77-1.46
Teacher advise 2	0.85	0.69-1.20	0.91	0.63-1.30
Teacher advise 3	0.79	0.57-1.08	1.02	0.75-1.38
Teacher advise 4	1.02	0.74-1.40	0.77	0.55-1.09

* significant at $p < .001$

*reference category: teacher advice medium prevocational

Prosocial subscale

Predictor	Age 13-14		Age 15-16	
	OR	95 % CI	OR	95 % CI
Underachievement	0.56	0.37-0.85	0.53	0.38-0.76*
Female gender	5.65	3.63-8.78*	4.75	3.20-7.06*
Non-Dutch ethnicity	1.02	0.66-1.59	0.98	0.64-1.48
Low affluence	0.84	0.25-2.82	1.19	0.36-3.93
Separated from one or both parents	0.77	0.50-1.18	0.82	0.55-1.23
Teacher advise 1	1.07	0.65-1.76	0.69	0.42-1.15
Teacher advise 2	1.45	0.61-1.20	0.84	0.49-1.43
Teacher advise 3	1.50	0.84-2.51	1.28	0.76-2.15
Teacher advise 4	2.49	0.92-2.43	1.43	0.83-2.49

* significant at $p < .001$

*reference category: teacher advice medium prevocational

4

Educational achievement in psychiatric patients and their siblings; a register-based study in 30,000 individuals in the Netherlands

Wanda M. Tempelaar MD, Fabian Termorshuizen PhD, James H. MacCabe MD PhD, Marco P.M. Boks MD PhD, René S. Kahn MD PhD

ABSTRACT

Background: Poor educational achievement is associated with a range of psychiatric disorders. Several studies suggest that this underperformance is due to cognitive deficits that commence before disease onset and reflect a genetic risk for this disorder. However, the specificity and the familial contribution of this cognitive deficit are not clear. We analysed lifetime educational achievement of psychiatric patients diagnosed with schizophrenia, bipolar or depressive disorder and their unaffected siblings.

Method: In a register-based case-control study, 1,561 patients with schizophrenia, 813 patients with bipolar disorder, 8,112 patients with depression, and their siblings were each matched with eight population controls. Patients, siblings and controls were compared on the highest educational stream they completed.

Results: Lower educational achievement was present in schizophrenia patients from primary school onwards (completing primary school: OR 0.69, completing secondary school: OR 0.69, completing academic education: OR 0.46), compared to patients with bipolar disorder or depression. Siblings of schizophrenia, bipolar or depressed patients showed no underachievement at primary or secondary school, but siblings of schizophrenia patients as well as siblings of depressed patients were less successful in their educational achievement after secondary school (completing academic education: schizophrenia siblings: OR 0.90, depressive disorder siblings: OR 0.91).

Conclusions: Educational underachievement from primary school onwards is specifically related to schizophrenia and not to bipolar disorder or depression. Moreover, it appears to be a harbinger of the illness, since it is not found in their siblings. These results add to evidence that early cognitive deficits are a distinct feature of the schizophrenia phenotype.

Keywords: psychiatric disorders, educational achievement, schizophrenia, bipolar disorder, depression

INTRODUCTION

Schizophrenia is associated with premorbid cognitive impairment¹⁻⁶. Prospective population studies have consistently shown that lower IQ prior to the onset of psychosis reflects an increased risk to develop schizophrenia^{1,2,4,7}. Poor school performance can be viewed as a broad measure of cognitive dysfunction since IQ is related to scholastic achievement⁸. Poor school performance has indeed been found to be associated with an increased risk of schizophrenia in several studies^{3,9-11} although not all studies on this subject found significant associations^{1,12}. Such scholastic (under)achievement may result from the underlying genetic vulnerability^{13,14} but can be influenced by neurodevelopmental¹⁵ and environmental factors such as socioeconomic status as well¹⁶. However, it is not clear whether premorbid cognitive deficits are specific for schizophrenia^{17,18}. For instance, studies of cognitive decline in bipolar disorder are inconclusive. Although premorbid cognitive deficits have been reported in patients with bipolar disorder^{19,20} a recent meta-analysis found no impairment in premorbid cognitive functioning in bipolar disorder as compared to schizophrenia¹⁸. In contrast to the multiple studies in schizophrenia and bipolar disorder, only a few have investigated the relationship between severe depression and premorbid cognition. Two large prospective cohort studies reported an increased risk for the development of schizophrenia and depression in individuals with lower childhood IQ^{21,22}.

Whether the reported cognitive impairments reflected in IQ and scholastic underperformance are changes due to the (early) effects of the illness, reflect neurodevelopment¹⁵ or are directly related to the (genetic) risk to develop the illness remains subject to debate. A role of familial susceptibility is suggested by studies showing that relatives of schizophrenia and bipolar patients have similar but less severe impairments in cognitive functioning as the patients^{10,23-25} and studies reporting impaired scholastic performance in schizophrenia offspring^{10,26}. Here, we investigate scholastic achievement of patients who developed schizophrenia, bipolar or depressive disorder and matched unaffected controls. Unique to this study is the inclusion of large groups of their siblings in order to investigate the relationship between familial vulnerability to these disorders and educational achievement.

METHOD

Study population and data-extraction

In this case-control study, we i) compared educational achievement of patients with schizophrenia, bipolar disorder and depression to educational achievement of matched controls and ii) compared educational achievement for siblings of these patients and sibling control groups. Data was collected from two different data sources: a psychiatric case registry and a national population database. The first data source is the Dutch Psychiatric Case Registry of the Middle Netherlands (PCR) serving the city of Utrecht and surrounding municipalities. The PCR contains anonymized information on all patients who attended any of the inpatient or outpatient mental health care facilities in this geographical area since 1999²⁷.

Data on all patients with a diagnosis of schizophrenia or non-affective psychotic disorder (DSM-IV codes 295.x, 297.x, 298.x, 293.8), patients with bipolar disorders (DSM-IV codes 301.13, 296.0x, 296.4x, 296.5x, 296.6x, 296.70, 296.8x) and depression (DSM-IV codes 296.2x, 296.3x, 300.4, 311) registered within the period January, 2000 until December, 2008 were extracted from the PCR databases. We refer to these groups as schizophrenia, bipolar or depressive disorder throughout this article. Cases diagnosed with both schizophrenia and bipolar disorder were categorized according their latest registered diagnosis. Additional analyses were conducted for a more restricted schizophrenia definition including only diagnoses of schizophrenia, schizophreniform or schizoaffective disorder. Data on educational achievement were collected from Statistics Netherlands, a national population database. Statistics Netherlands produces community statistics and is responsible for collecting and processing data to be used in daily practice, by policymakers and for scientific research²⁸. All legally residing citizens of the Netherlands are registered with several sociodemographic and household characteristics. From 1995, information on education is stored in the national database, although educational data is far from complete since data were mostly collected in random surveys. From 2003 onwards, educational data are directly collected from the educational institutions and their monitors as well. This results in multiple sources of data on educational tracks, ranging from enrolment in educational institutions, applications for scholarship or results on national exams. Psychiatric cases were linked to the Statistics Netherlands registry based on date of birth, gender and postal code²⁷.

Data on educational achievement was missing for most patients, for 26% of the schizophrenia patients (N = 1,561 from a total of 6,004), 32.8% of the bipolar patients (N= 813 from a total of 2479) and 35.3% of the depression patients (N= 8,112 from a total of 22,988) it was possible to obtain information on educational achievement in the population register.

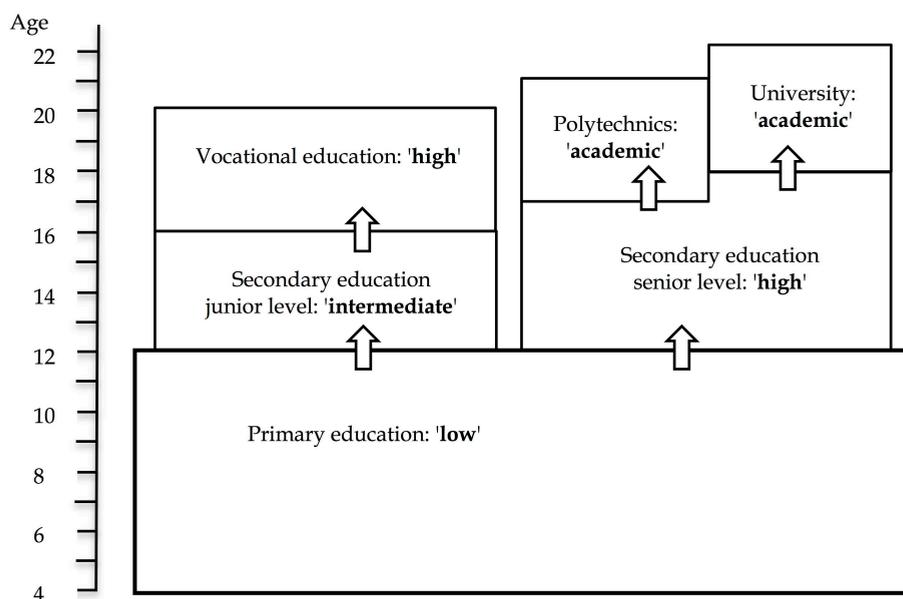
Control selection

For each individual patient, (maximum) eight random controls were matched using year of birth, gender, country of birth, region of residence and source of educational information. All cases from the PCR were excluded from the pool of potential controls to avoid any psychiatric disorder in the controls.

Educational achievement

In the Netherlands, education is compulsory from age five until the age of 16. State schools provide primary, secondary and almost all further education. The Dutch education system consists of eight years of primary education, four to six years of secondary education (depending on the type of school) and two to six years of higher education (depending on the type of education). In higher education there is a distinction between vocational education and science-oriented education. In primary school, every pupil receives the same education. After primary school, the pupils enter secondary school at age 12 in one of the four different streams of secondary education: low, intermediate and high preparatory vocational and pre-university. These different streams are illustrated in Figure 1.

Figure 1: School system in the Netherlands



Each stream demands increasing intellectual and scholastic abilities²⁹. In the Dutch population the mean IQ among students in the ‘low preparatory vocational’ stream is 92.0 (SD 11.7), intermediate preparatory vocational stream is 98.1 (SD 9.2), high preparatory vocational stream is 106.9 (SD 10.6) and preparatory university is 115.6 (SD 11.8)³⁰. At the end of secondary school, all pupils take national state exams at their respective level and pupils who pass those exams may enter further education in the three follow-up streams: vocational education (54% of all pupils), polytechnics (28% of all pupils) or university (18% of all pupils)³¹.

In this study we compiled four levels of educational achievement: 1) ‘low’: primary education (eight years of education), 2) ‘intermediate’: low and intermediate preparatory vocational education (twelve years), 3) ‘high’: high preparatory vocational education, preparatory university and vocational education (13-14 years), and 4) ‘academic’: polytechnics and university (>14 years of education) (Figure 1). Participants who finished primary education at most and did not finish a stream of education higher than primary education were classified as ‘low’ etc. International equivalents of the degrees in these different streams are shown in Table 1.

Table 1. Dutch qualifications compared to international standards.

Degree or qualification in US	Dutch equivalent	EQF* level
General Educational Development diploma	Secondary education junior level diploma	2
High School diploma	Secondary education senior level diploma	4
Associate’s degree (terminal/vocational)	Vocational education degree	4
Associate’s degree (transfer program)	Associate degree or secondary education senior level	4-5
Bachelor’s degree	Bachelor’s degree Polytechnics / University	6
Master’s degree	Master’s degree Polytechnics / University	7

EQF = European qualifications framework: international system that compares national qualifications and educational levels across different countries in Europe. (www.epnuffic.nl)

Analysis

Data-management, record linkage and statistical analyses were performed in SPSS, version 20.0.

First, baseline characteristics were summarised using descriptive statistics. Patients and controls were compared with respect to the highest educational stream completed. To examine whether educational achievement was related to psychiatric disorder we created three different dichotomizations of the four

ordered levels of educational streams: academic versus the three lower levels, academic and high versus intermediate and low, and lastly the highest three levels versus low (i.e. higher than primary school versus primary school at most). The proportions of patients and controls with high educational achievement in these dichotomies were compared in a multivariable ordinary logistic regression model. In other words: we analyzed the odds for passing to a next level of education separately for each of these three thresholds. Each threshold dichotomizes educational outcome as higher than that threshold compared to completed education lower than that threshold. Odds ratios smaller than one indicate a lower achievement in patients compared to matched controls. The estimated OR's and 95%-CI's were adjusted for the stratification factors used for matching: source of educational data, age, gender, ethnicity and whether the municipality of residence was in the catchment area of the PCR³². Similar analyses were performed for the siblings of the patients with their matched controls. We included a random effect taking account of clustering within families in a random intercept logistic regression model. Finally, we analysed educational achievement of the more restricted definitions of patient groups.

RESULTS

Study population (table 2)

The original sample of the Dutch Case Registry consisted of 31,471 patients: 6,004 diagnosed with schizophrenia, 2,479 with bipolar disorder and 22,988 with depressive disorder. For 10,486 patients (33.3%) it was possible to retrieve information on educational achievement. Among the patients with information on educational achievement mean age was lower compared to the total sample: 31.7 (SD 11.4) versus 45.9 (SD 18.1) years for schizophrenia patients, 35.0 (SD 11.4) versus 49.9 (SD 14.9) for bipolar disorder and 29.6 (SD 13.1) versus 46.6 (SD 16.5) in depressive disorder. The proportion of males was higher among patients with information on education in schizophrenia (62.3% versus 55.6%) but not in bipolar disorder and depression (bipolar disorder: 42.7% versus 45.0%, depressive disorder: 32.2% versus 36.1%). The proportion of Dutch natives was also higher among schizophrenia patients compared to those without (70.3% versus 64.7%) but not in bipolar disorder and depression (bipolar disorder: 82.5% versus 83.4%, depression: 73.5% versus 71.7%).

Table 2: demographic characteristics in patients groups

	Schizophrenia	Bipolar Disorder	Depressive Disorder
Gender (N,%)			
Male	971 (62.2%)	347 (42.7%)	2615 (32.2%)
Female	590 (37.8%)	466 (57.3%)	5497 (67.8%)
Age (N,%)			
<25.6	544 (34.8%)	184 (22.6%)	3741 (46.1%)
25.6-34.7	480 (30.8%)	251 (30.9%)	1884 (23.3%)
34.7-43.8	306 (19.6%)	197 (24.2%)	1279 (15.8%)
43.8-55.0	169 (10.8%)	134 (16.5%)	831 (10.2%)
>55.0	62 (4.0%)	47 (5.8%)	377 (4.6%)
Age (mean, SD)	31.7 (11.4)	35.0 (11.4)	29.6 (13.1)
Ethnic origin (N,%)			
Native Dutch	1098 (70.3%)	671 (82.5%)	5959 (73.5%)
From Other Western Countries	161 (10.3%)	87 (10.7%)	753 (9.3%)
Turkish-Dutch	44 (2.8%)	5 (0.6%)	270 (3.3%)
Morrocan-Dutch	55 (3.5%)	11 (1.4%)	454 (5.6%)
Surinamese / Antilean-Dutch	93 (6.1%)	20 (2.5%)	234 (2.9%)
Other non-Western countries	110 (7.0%)	19 (2.3%)	442 (5.4%)
Total (N,%)	1561 (26.0%)	813 (32.8%)	8112 (35.3%)

Table 3. Patients' stream of education

Level of education	Schizophrenia		Bipolar disorder		Depressive disorder	
	Patients N (%)	Controls	Patients	Controls	Patients	Controls
Low	191 (12.2%)	1111 (9.0%)	37 (4.6%)	302 (4.7%)	1199 (14.8%)	9147 (14.4%)
Intermediate	85 (5.4%)	531 (4.3%)	11 (1.4%)	91 (1.4%)	388 (4.8%)	2163 (3.4%)
High	837 (53.6%)	5308 (43.1%)	374 (46.0%)	2347 (36.4%)	4071 (50.2%)	28242 (44.5%)
Academic	448 (28.7%)	5359 (43.5%)	391 (48.1%)	3715 (57.6%)	2454 (30.3%)	23951 (37.7%)
Total (N)	1561	12309	813	6455	8112	63503

Table 4. Multivariable logistic regression patients vs matched controls

Level of education	Schizophrenia	Bipolar disorder	Depressive disorder
threshold	OR [95%-CI]	OR [95%-CI]	OR [95%-CI]
Above lowest	0.69 [0.58-0.83] ^a	1.03 [0.72-1.49]	0.99 [0.93-1.06]
Above intermediate	0.69 [0.59-0.80] ^a	1.04 [0.75-1.43]	0.90 [0.84-0.96] ^b
Above high	0.46 [0.41-0.53] ^a	0.65 [0.56-0.76] ^a	0.68 [0.64-0.71] ^a

^a P<0.001, ^b P<0.01

Table 5. Siblings' level of education

Level of education	Schizophrenia		Bipolar disorder		Depressive disorder	
	Siblings N (%)	Controls N (%)	Siblings N (%)	Controls N (%)	Siblings N (%)	Controls N (%)
Low	687 (17.1%)	3306 (16.8%)	125 (8.0%)	668 (8.6%)	2874 (19.8%)	14598 (20.4%)
Intermediate	1769 (44.1%)	801 (4.1%)	32 (2.1%)	190 (2.4%)	703 (4.9%)	2718 (3.8%)
High	1366 (34.1%)	8533 (43.4%)	667 (42.8%)	3372 (43.5%)	6592 (45.5%)	31513 (44.1%)
Academic	1366 (34.1%)	7003 (35.7%)	734 (47.1%)	3526 (45.5%)	4319 (29.8%)	22571 (31.6%)
Total (N)	4007	19643	1558	7756	14488	71400

Table 6. Multivariable logistic regression siblings vs. matched controls

Level of education	Schizophrenia	Bipolar disorder	Depressive disorder
threshold	OR [95%-CI]	OR [95%-CI]	OR [95%-CI]
Above lowest	0.99 [0.90-1.09]	1.11 [0.90-1.36]	1.05 [1.00-1.11] ^b
Above intermediate	0.96 [0.88-1.05]	1.14 [0.94-1.38]	0.98 [0.94-1.03]
Above high	0.90 [0.82-0.99] ^b	1.09 [0.97-1.22]	0.91 [0.87-0.95] ^a

^a P<0.001, ^b P<0.05

OR signify odds ratios for level of education above the threshold

Chapter 4

The baseline characteristics of the participants are presented in table 2. The study population consisted of 10,486 patients: 1,561 diagnosed with schizophrenia, 813 with bipolar disorder and 8,112 with a depressive disorder.

Educational achievement patients and controls (table 3, 4)

Multivariable analysis of the association of schizophrenia with educational achievement showed that the odds of achieving streams of education higher than primary education (ie, completing primary school at the age of 12) was significantly lower in schizophrenia patients compared with their matched controls (OR 0.69, 95% CI: 0.58-0.83). This educational underachievement was also present at higher streams, ie completing intermediate, high or academic levels of education. Bipolar disorder patients and controls had no differences in odds to complete low, intermediate or high levels of education, but odds for completing academic education were significantly lower in bipolar patients (OR 0.65, 95% CI 0.56-0.76). Odds for patients with depression were not different for completing low level of education (ie primary education) but odds for completing intermediate level of education were slightly lower (OR 0.90, 95% CI 0.84-0.96) and odds for completing academic education were considerably lower (OR 0.68, 95% CI 0.64-0.71) compared to controls.

Educational achievement in siblings (table 5, 6)

Siblings of schizophrenia patients showed no difference in odds of completing educational achievement at low, intermediate or high level (primary and secondary school, vocational education), but the odds of achieving academic education was slightly but significantly lower (OR 0.90, 95%CI 0.82-0.99) as compared with their matched control siblings. Siblings of bipolar disorder patients had no significant differences in educational achievement at any level compared with matched controls. Siblings of depressed patients showed slightly higher odds for completing low education (OR 1.09, 95% CI 1.02-1.16) and a slightly decreased rate of achieving academic education (OR 0.87, 95% CI 0.83-0.92).

Post-hoc analysis

Additionally, we analysed educational achievement using a more restricted definition of schizophrenia including only schizophrenia, schizophreniform or schizoaffective disorder patients (N=860 instead of N=1,561). These results were roughly the same, but even more pronounced, as reported above: multivariable analysis compared with matched controls showed that the schizophrenia patients performed worse at low level of education (primary school): OR 0.59, 95% CI 0.46-0.76), at intermediate level OR 0.68, 95% CI 0.54-0.85 and at academic

education: OR 0.37, 95% CI 0.31-0.43 (results not presented in table). Restricting our analyses to the cases of bipolar I disorder and major episodes of depression (classified as severe major single episode or major recurrent episodes) also yielded comparable results: no significant differences in odds for low, intermediate or high level education, where odds for achieving academic education were lower (bipolar disorder: OR 0.62, 95% CI 0.51-0.75 and depressive disorder: OR 0.70, 95% CI 0.64-0.76). Restricting our analyses to participants aged 25 and older also yielded similar results.

To investigate the potential influence of comorbid diagnosis of childhood disorders or mental retardation, we checked for DSM axis-II diagnosis of mental retardation and any childhood DSM axis-I diagnosis (such as pervasive developmental disorders or attention deficit hyperactivity disorder). In total, 143 patients were diagnosed with any childhood psychiatric disorder or mental retardation. Excluding these patients from the original analysis did not change the results substantially; odds ratios in schizophrenia patients remained lower for achieving all levels of education (low education OR 0.74, 95% CI 0.61-0.90, intermediate education OR 0.75, 95% CI 0.63-0.88, academic education OR 0.45, 95% CI 0.40-0.52).

DISCUSSION

In this registry based case-control study in over 30,000 patients and their siblings our results show that patients with schizophrenia, in contrast to patients with bipolar disorder or depression, underachieved from primary school onwards compared with their matched controls. These findings are in keeping with previous reports showing that cognitive impairment and poor educational performance before disease onset is a distinct feature of schizophrenia and not of affective disorders such as bipolar disorder and depression^{3,5,33}. Moreover, it appears to be a harbinger of the illness itself, since cognitive underachievement in childhood or adolescence is not found in their siblings. Our results replicate previous findings showing that impairments in educational achievement occur as early as in primary school (age 6-12) and support the neurodevelopmental hypothesis of schizophrenia stating that (minor) deficits in cognition and behaviour are seen many years before illness onset^{5,23,34,35}.

Furthermore, our results demonstrate that patients with schizophrenia, bipolar disorder or depressive disorder show more underachievement in further education. This is consistent with previous findings and could be influenced by early symptoms of the illness^{36,37} since the age range of students at further education overlap with the age range of onset of schizophrenia, bipolar disorder and depressive disorder.

Educational achievement at primary or secondary school was not impaired in siblings of patients with schizophrenia compared with their matched controls, but we found a small risk of failing to complete academic education. This is line with recent study by Kendler et al. who concluded that common genetic or familial-environmental effects only marginally confounded the association between scholastic achievement in adolescence and siblings of patients with schizophrenia¹¹.

Interestingly, our results show that siblings of bipolar patients performed better at all levels of education, although these findings did not reach statistical significance. This finding is in agreement with previous findings where it was found that higher educational attainment was associated with increased risk for bipolar disorder⁹, as well as with results from our recent study in clinical cohorts that showed that, although bipolar patients had a lower IQ than unaffected controls after disease onset, they were more likely to have completed the highest level of education⁶. This contrasts with schizophrenia patients, who showed both intellectual and educational deficits compared to unaffected controls^{3,6,9}. These findings on educational underachievement in patients with schizophrenia might be used to improve early detection, for instance scholastic underperformance combined with a family history with schizophrenia or other prodromal signs of schizophrenia may warrant further assessment of the child or adolescent.

Strengths and limitations

Several properties of this study limit the generalization of our findings. First is the large amount of missing data on educational achievement of psychiatric patients in the database of Statistics Netherlands. Patients with absent information on education are considerably older than the patients with information on their educational tracts, due to lack of automatized data gathering before 2003. Also several participants are not yet 25 years old, and may still attend education. There is no reason that this should lead to bias in our results since we matched on age, but we cannot be sure our conclusions hold for earlier generations. Secondly, we analysed data on completed education and not in detailed time-intervals or current educational efforts. Therefore, precise inferences are not possible regarding the timing of underachievement or failing of passing to a next level of education. Thirdly, our data were gathered from mainstream schools, excluding special needs education. Thus, results are not suitable to generalize to patients who are excluded from mainstream educational systems, such as patient with learning difficulties, severe somatic illness or severe child psychiatric disorders, although including them would probably strengthen our results. Furthermore, we could not investigate the influence of clinical characteristics such as the distinction between bipolar disorder patients with or

without psychotic symptoms^{38,39}. Moreover, residual confounding by for instance socio-economic status cannot be excluded, although the data are generated from an epidemiological representative regional resource. We noticed that our study population included fewer patients with bipolar disorders than would be expected on the basis of the reported prevalence in the general population⁴⁰. This might be due to an attribution bias, where only the more severe cases of bipolar disorder are registered or bipolar disorders are diagnosed as major depressive disorders.

Strengths of our study include the fact that it is based on a large geographically representative sample of patients that included admitted as well as outpatients. Data are obtained from a reliable source, not self-reported or subject to recall bias.

In summary, our results show educational underachievement in patients with schizophrenia as early as primary school but not in their siblings. These results replicate previous findings that early cognitive dysfunction is related to the development of schizophrenia. Absence of early educational underachievement in siblings of schizophrenia patients and patients with bipolar illness and major depression suggest that this cognitive deficit is a harbinger of schizophrenia.

Acknowledgement

The authors thank Statistics Netherlands (Centraal Bureau voor de Statistiek, CBS) for kindly providing the data necessary for the study.

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5

The Dutch bipolar offspring study; cognitive development and psychopathology

Wanda M. Tempelaar MD, Esther Mesman PhD, Manon H.J. Hillegers MD PhD

In preparation for submission

ABSTRACT

Background: It has long been suggested that cognitive deficits were not associated with bipolar disorder, but over the last decade a growing number of studies reported cognitive impairments in bipolar patients, even during periods of euthymia and in unaffected relatives. Currently various aspects of the relationship between cognitive impairment and bipolar disorder are not clear yet. Studying cognitive functioning in offspring at familial risk for bipolar disorder could improve our understanding of the association between cognitive functioning and onset and course of psychopathology. We therefore investigated cognitive and educational functioning prospectively in an at-risk population: children of patients with bipolar disorder.

Method: Bipolar offspring (N=92) from the prospective Dutch bipolar offspring study were evaluated within a longitudinal context at adolescence and adulthood for IQ estimate, educational achievement and development of any psychiatric disorder. The main outcome measure was change in IQ estimate between baseline assessment (at adolescence) and after 12 years follow-up (at adulthood).

Results: Multivariable linear regression analyses showed that a diagnosis of any mood disorder by early adulthood, including bipolar disorder (N=13) and unipolar mood disorder (N=40), was not related to larger decline in estimate of cognitive ability compared to unaffected offspring. Age at onset of any psychiatric disorder at or before age 16 years was significantly related to a lower IQ estimate at adulthood. Poor educational underachievement was not associated with psychopathology or estimate of cognitive ability in bipolar offspring compared to unaffected offspring.

Conclusions: A larger decline in cognitive functioning was found in bipolar offspring who develop psychopathology at a young age (<16 years), as compared to offspring who develop psychopathology later in life or no psychopathology. This change in measured IQ was not reflected in lower educational achievement. This possible aberrant cognitive development in bipolar offspring may be a sign of underlying vulnerability for impaired neurodevelopment that could be associated with expression of early psychiatric symptoms or a direct illness related effect.

Keywords: Vjdc`Uf`XjgcfXfz`cZgdf|b|žW|b|hj`Y`Xy`Ycda`Yblž`Ež`Yxi`W|hcbU`ac\|Yj`Ya`Ybh

INTRODUCTION

Bipolar disorder (BD) is a severe mental illness characterized by recurrent episodes of depression and mania in alternation with periods of euthymia and/or subsyndromal mood episodes. Numerous studies in BD patients reported impairment of neuropsychological domains^{1,2}. However, results regarding intelligence (IQ) in patients with BD are inconsistent and the impact of other factors such as duration of illness, number of episodes and medication is still under debate³⁻⁵. This indicates that the onset and course of cognitive impairment in BD patients is less clear, in contrast to current knowledge on cognitive decline in relation to the development of psychosis. In patients with schizophrenia (SZ), a decline in both cognitive and educational functioning is seen prior to the onset of the first psychotic episode⁶⁻⁸. This impairment remains relatively stable during the illness, independent of psychotic symptoms^{9,10}. In BD, some studies show neurocognitive impairment during acute episodes¹¹, whilst other studies describe poorer cognitive functioning in both first episode-, euthymic- and chronic patients; in bipolar type I and type II patients; and first-degree BD relatives^{5,12,13}. Regarding onset, longitudinal studies in BD patients show preserved premorbid intelligence and neuropsychological functioning^{5,14} although it has also been suggested that subtle neuropsychological impairment may exist prior to illness onset¹⁵. Findings on educational achievement in BD are inconsistent as well; recently a large prospective study found an association between development of BD and poor scholastic achievement¹⁶ and a higher risk for school-termination prior to completion^{17,18}. However, some studies show normal or high educational achievement prior to the onset of BD^{19,20}. Overall, these findings on cognitive and educational parameters before illness onset suggest that neurodevelopmental abnormalities occur in SZ but not necessarily in BD. However, methodological differences between these studies including possible modifying factors i.e. symptomatology and current episode, comorbidity, age at onset, illness severity and duration, hamper interpretation of these study results. One potential modifying factor that is associated with a poor outcome in both SZ and BD is early onset of the disease^{21,22}. It is hypothesised that earlier age at onset has a more disruptive impact on brain maturation during critical developmental phases²³. From a developmental point of view it is therefore important to take age at onset into account when investigating the relationship between BD and cognitive performance.

So far, a limited number of studies show that unaffected first-degree family members of bipolar patients already have modest cognitive and neuropsychological impairment^{2,20,24}. Therefore cognitive impairment may represent a vulnerability marker rather than a consequence of the disease. Cognitive impairment as a vulnerability marker may be useful in improving early detection of BD or a target for early intervention and contribute to improvement of functioning in BD patients²⁵⁻²⁸.

Since the incidence of the BD in the general population is around 1-2%²⁹, a prospective study among unaffected children of a parent affected with BD (BD offspring) is needed to understand cognitive trajectories during psychopathology development. Indeed, BD offspring have a 10 times increased risk to develop BD, 4 times increased risk to any mood disorder and 2.7 times increased risk to develop other psychopathology³⁰⁻³³. So far, few studies investigated cognitive functioning in bipolar offspring and only half of them had a prospective design³⁴⁻³⁶. Three studies reported significantly lower IQ in bipolar offspring than in healthy controls³⁵⁻³⁷ whereas others^{34,38,39} have shown no difference in IQ in bipolar offspring. Of note is that some of these studies excluded offspring with psychopathology^{36,37}, or corrected for this in the analysis³⁴ and others^{35,38,39} included offspring regardless of past or current psychopathology. In the present study we prospectively examined the course of general cognitive ability and educational achievement in BD offspring from adolescence to early adulthood. First, we investigated an estimation of cognitive ability and educational achievement in offspring who developed BD during follow-up. Second, we examined whether other psychopathology in offspring showed similar associations with cognitive and educational functioning or different cognitive trajectories. Furthermore, we explored whether the effects of other variables on cognitive ability, e.g. age at onset, could explain a possible association.

Knowledge on the pattern of cognitive and educational functioning in bipolar offspring will add to the understanding of neurodevelopmental underpinnings of BD and ultimately may contribute to improved identification and intervention in individuals at risk.

METHOD

Population and Procedure

Participants originated from the Dutch Bipolar Offspring Study, a longitudinal fixed cohort study established in 1997^{31,40-42}. Study design and recruitment procedure are described in detail elsewhere⁴⁰. In short, 140 offspring (ages 12-21 years) from 86 families with one bipolar parent (74% bipolar I; 26% bipolar II)

The Dutch bipolar offspring study; cognitive development and psychopathology were recruited through the Dutch Association for Manic Depressives and Relatives (62 families; 102 children) and through outpatient clinics in nine psychiatric hospitals (24 families; 38 children). DSM-IV diagnoses of bipolar I and II disorders in parents were confirmed by face-to-face interviews using the International Diagnostic Checklist⁴³ and by the clinical diagnosis of the treating psychiatrist⁴⁰. Exclusion criteria for offspring were a severe physical illness or handicap or an intelligence quotient below 70. Offspring were assessed at baseline and after one, five and 12 years by trained psychologists or psychiatrists^{31,40-42}. The current study focuses on the 108 (77.1%) participants that were followed for the full 12 years. The psychiatric status of the offspring was evaluated at each follow-up assessment according to DSM-IV Axis I criteria using the Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version 44 or after the age of 18 years by using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)⁴⁵. BD not otherwise specified (BD-NOS) was not assessed. Details on demographic characteristics and lifetime psychopathology at the 12-year follow-up assessment are described by Mesman et al³¹. The Medical Ethics Committee of the University Medical Center Utrecht approved the study. Written informed consent from both the offspring and their parents was obtained.

Cognitive assessment

At baseline and 12 year follow-up, an estimation of general intellectual ability was calculated based on the scores on the two subtests, vocabulary and block design, on the age-appropriate Dutch version of the Wechsler Intelligence Scale. This abbreviated 2-subtest form of the Wechsler Adult Scale of Intelligence (WAIS) shows high reliability (0.93) and correlates well with Full Scale IQ (0.88-0.89)⁴⁶. At baseline measurement 56 participants were aged under 18 and were assessed using the Wechsler Intelligence Scale for Children-Revised (WISC-R), 36 participants completed the subtests of the Wechsler Adult Scale of Intelligence (WAIS-III). Raw and norm scores were calculated according to rules set forth in the WISC / WAIS Manuals^{47,48}. Of note is that eight offspring were taking medication at the time of follow-up assessment; five participants used a mood stabilizer (mostly lithium), three participants used antidepressants, two participants used a benzodiazepine and one participant used methylphenidate.

Educational achievement

All participants completed the Bedford College Life Events and Difficulties Schedule (LEDS) at each assessment^{49,50}. The LEDS is a semi-structured interview, which assesses life events and difficulties the participants encountered during the past years, including education-related events such as finishing degrees or terminating school prior to completion^{51,52}. All interviewers were trained to assess LEDS.

All LEDS interviews were screened for any events related to education⁵³. We scored poor educational achievement as: decline in educational level, grade retention or early school termination. Early school termination was classified when participants left school without completing graduation. This could also be temporary, for instance when participants quit school and started another study one or several years later.

Data preparation

Of the 108 offspring followed for 12 years, one participant did not participate in the cognitive tests at baseline assessment and 15 did not participate in the cognitive tests at adulthood, resulting in a study population of 92 participants. Analyses of the missing data showed no differences between participants with or without missing data including missing IQ at follow-up assessment.

We assessed the numbers and percentages of offspring diagnosed with bipolar spectrum disorders, unipolar mood disorders (major depressive disorder, depressive disorder NOS, dysthymia and adjustment disorder with mood characteristics), any mood disorder (bipolar spectrum disorders and unipolar mood disorder combined) and other disorders (ADHD, alcohol/substance use disorders, anxiety disorders, disruptive behavioral disorders, eating disorders, encopresis, enuresis, pervasive developmental disorder and sleeping disorders). We classified participants in dummy variables according their psychiatric status at assessment in adulthood, thus taking into account the presence of comorbidity. Age at onset (of first disorder) was dichotomized into early onset (≤ 16 years) and late onset (>16 years or no disorder).

For 76 offspring (82.6%) it was possible to retrieve information on educational achievement. Among the participants without information on educational achievement there were significantly more participants diagnosed with a disorder (any disorder: 81.3%) compared to the total sample (any disorder 72.8%). This was especially true for mood disorders; 81.3% of the participants without information were diagnosed with any mood disorder versus 53.3% of the total sample.

Statistical Analysis

Data-management, record linkage and statistical analyses were performed in SPSS, version 23.0.

To investigate the course of cognitive functioning we calculated the difference in IQ estimation between assessment at adulthood and adolescence. We performed a multivariable linear regression analysis to investigate the association of change in IQ estimate with bipolar disorder, unipolar disorder and other disorders

compared with participants who had no psychiatric diagnosis during the entire 12 year follow-up period ('resilient') as a reference group. Subsequently, similar analyses were performed to investigate the effect of possible modifying factors. We first added age at onset to the model, next 'baseline IQ estimate' and then lifetime number of diagnoses. Post hoc, interaction effects between disorder and age at onset were investigated. Logistic regression analyses were used to investigate the association between poor educational achievement and psychopathology with the 'resilient' outcome group as a reference group. Age and gender were entered as covariates in all models.

RESULTS

Study population

Table 1 presents the baseline characteristics of the study population. Mean age at baseline measurement was 16 years old and gender was about equally distributed. Overall, lower mean IQ estimates were observed in follow-up measurement compared to baseline measurement ($T = -5.06, p = 0.00$) (Table 1).

IQ estimate and disorders

Multivariable linear regression analysis showed a significant association between any lifetime diagnosis and lower IQ estimate at adulthood (standardized beta $-.24, p = 0.02$; $F(3, 88) = 3.756, p = 0.01, R^2 .113$). Multivariable linear regression analysis showed no significant association between change in IQ estimate and bipolar disorder (Table 2a). A significant association was found between change in IQ estimate and offspring developing non-mood disorders: 'other disorder' (standardized beta $-.28, p = 0.01$).

Table 1. Characteristics of study population

	All participant N = 92 (%)	No disorder* N = 25	Any disorder N = 67	Bipolar septru N = 13	Unipolar dipr N = 40	Other disorder N = 49
Male gender	51 (54.8%)	13 (52.0%)	38 (56.7%)	7 (53.8%)	19 (47.5%)	29 (59.2%)
Mean age at baseline	15.9 (SD 2.7)	15.6 (SD 3.0)	16 (SD 2.6)	15.9 (SD 2.9)	15.9 (SD 2.4)	16.2 (SD 2.6)
Mean IQ estimate at baseline	114.5 (SD 14.7)	114.4 (SD 9.4)	114.6 (SD 16.3)	115.9 (SD 16.2)	110.3 (SD 15.5)	116.7 (SD 15.2)
Mean IQ estimate at adulthood	107.7 (SD 15.7)	112.8 (SD 14.8)	105.9 (SD 15.7)	105.9 (SD 18.3)	104.0 (SD 14.9)	106.7 (SD 15.3)
Educational underachievement	40 (52.6%)	11 (50.0%)	26 (51.0%)	6 (66.7%)	16 (55.2%)	25 (59.5%)
missing	16 (17.4%)	3 (12.0%)	13 (19.4%)	4 (30.8%)	11 (27.5%)	7 (14.3%)

SD = standard deviation

* There were no significant differences in gender, age, mean IQ scores and raw subtests scores between No disorder and Any disorder.

Other disorder include: ADHD, alcohol/substance use disorders, anxiety disorders, disruptive behavioral disorders, enuresis, eating disorders, enuresis, pervasive developmental disorder and sleeping disorders.

Table 2a. Linear regression model with disorders

Model: $R^2= 0.171$, $F= 3.542$, $P\text{-value}= 0.01$

Variable	Coefficient	SE(Coefficient)	Standardized beta	t-ratio	P-value
Gender	2.65	2.51	0.11	1.06	0.29
Age at baseline	-1.21	0.46	-0.26	-2.66	0.01
Bipolar disorder	-0.45	3.53	-0.01	-0.13	0.51
Unipolar disorder	3.76	2.60	0.15	1.45	0.15
Other disorder	-7.02	2.57	-0.28	-2.73	0.01

Dependent: change in IQ estimate. Predictors: disorder category indicators, controlled for Age and Gender (male). Reference group is the No disorder category.
SE = standard error

Table 2b. Linear regression model including modifiers

Model: $R^2= 0.252$, $F= 4.783$, $P\text{-value}= <.001$

Variable	Coefficient	SE(Coefficient)	Standardized beta	t-ratio	P-value
Gender	4.85	2.50	0.19	1.94	0.06
Age at baseline	-0.59	0.48	-0.01	-1.22	0.23
IQ at baseline	-0.28	0.09	-0.32	-3.18	0.00
Age at onset ≤ 16 vs >16	-6.51	3.02	-0.25	-2.16	0.03
Mood disorder	1.14	2.61	0.04	0.44	0.66
Other disorder	-2.41	2.93	-0.09	-0.82	0.41

Dependent: change in IQ estimate. Predictors: disorder category indicators, Age at onset, controlled for Age and Gender (male). Reference group is the No disorder category.
SE = standard error

We then investigated to what extent these findings could be attributed to other factors possibly associated with cognitive development: age at onset, IQ at baseline, and number of diagnoses. Age at onset at or before 16 years old was significantly associated with larger decline compared to age at onset older than 16 years and resilient offspring (standardized Beta -0.24, $p= 0.05$). The association between Other disorder and change in IQ estimate attenuated. When IQ estimate at baseline was added to this model (Table 2b), age at onset remained significantly associated (standardized Beta -0.25, $p= 0.03$) and lower IQ estimate at baseline was also significantly associated (standardized Beta -0.28, $p= 0.00$). Number of disorders was not significantly associated with the outcome. There was also no significant interaction effect between disorder and age of onset.

Educational achievement

Regarding educational achievement: 12 participants (13.0%) declined to a lower educational level, 24 participants (26.1%) repeated a grade and 40 participants

(43.5%) quit school without completion. There was considerable overlap between these groups: five participants were reported both downgrading, repeating a grade and stopped attending school; 17 participants both repeated a grade and stopped attending school and seven participants both downgraded and stopped attending school.

Multivariable logistic regression analyses showed no significant associations between poor educational achievement and development of any mental disorder, decline in IQ estimate or age at onset (Table in supplement).

DISCUSSION

To our knowledge, this is the first prospective cohort study investigating the association between the course of general intellectual ability and psychopathology in offspring of patients with BD. Our main finding is that cognitive outcome decreases more in those BD offspring who develop psychopathology early in life (≤ 16 years), as compared to offspring who develop psychopathology after age >16 years or have no psychopathology after 12 years follow up.

We found no specific association between mood disorders (BD and UD) and cognitive functioning. Those offspring diagnosed with any 'Other disorder', scored significantly lower on IQ estimate in adulthood. Most of these participants were affected with developmental disorders with an early age of onset, and the effect attenuated when age at onset was added to the model. This finding added to the importance of age of onset of psychopathology and the development and course of cognitive functioning in high-risk offspring.

Our finding that psychopathology with an early age of onset was associated with lower IQ estimate at adulthood assessment can be viewed in the same context as previous research showing that individuals with psychiatric disorders with an onset in childhood or adolescence, often experience a more chronic and serious course of illness with poorer prognosis⁵⁴⁻⁵⁶. This finding was also reported in a study of Bearden and colleagues showing that youth with an earlier age at onset of BD showed greater impairment in neuropsychological functioning²³. These data indicated no effect of duration of illness, suggesting that earlier age at onset may be associated with greater disruption in brain development thus leading to the observed greater neuropsychological impairment²³. Unfortunately, due to the low prevalence of BD with early age at onset in our study we were not able to confirm this finding. In addition, Jepsen et al described that children and adolescents with early onset SZ seemed to stagnate in cognitive development (IQ), suggesting aberrant age-related acquiring of new information and skills⁵⁷. In contrast with results from our study, these studies report on cognitive impairment

associated with early onset of symptoms of the same disorder whereas our study showed an association in offspring at familial high-risk with early onset of any psychopathology. There are several hypotheses regarding the mechanism behind this finding. First, the results may indicate that those offspring who develop any illness at early age constitute those individuals of particularly high liability for impaired brain development with a vulnerability to both psychiatric and cognitive symptoms¹². A psychiatric disorder at early age may be a first sign of this aberrant brain development with associated impaired cognitive ability as an expression of this process. Second, our finding of possible aberrant cognitive development in bipolar offspring could reflect an illness related effect, but interestingly not a deteriorating effect of BD but of any mental illness. Particularly in individuals with high genetic liability (BD offspring), a disruption (any psychiatric disorder) during particularly sensitive periods of brain development (childhood and early adolescence) may be associated with further disruptions in brain development, even when the 'first' disruption has subsided^{12,23}. Regarding other potential modifiers that could influence the relationship between psychopathology and general cognitive ability, the data illustrate that a low IQ at baseline was significantly related to a stronger decline in cognitive outcome at adulthood. Due to a relatively small sample size further exploration of this finding such as possible interaction effects was not feasible. A premorbid decline in cognitive functioning already preceding the baseline assessment of cognitive ability in those BD offspring with a worse outcome cannot be ruled out. Surprisingly no effect of number of disorders was found, suggesting that having one or multiple disorders does not influence the course of general cognitive ability in this sample. This is partly in contrast with previous studies describing an association between number of mood episodes and cognition in adults with BD^{3,4} but this may be a specific effect of mood episodes or illness progression. No such relationship was described in youth literature but this is hard to investigate since bipolar youth experience shorter illness duration with fewer mood episodes.

With respect to potential effects of comorbidity in bipolar youth it was recently reported that greater neuropsychological impairments occur in bipolar youth who suffer from comorbid attention deficit hyperactivity disorder (ADHD)⁵⁸. Due to the low prevalence rate of ADHD in our sample we were not able to confirm this.

Our exploration of a possible association between poor educational achievement and psychopathology in BD offspring was not confirmed, however hampered by incomplete data.

Strengths and limitations

The main strengths of this study are its long follow-up, detailed clinical assessments and high retention rate. Although this is one of the largest and longest BD offspring cohorts, this study should be interpreted with consideration of several limitations. First, there was no healthy control group and typical development of cognition could not be controlled for. Second, the relatively small sample size did not allow power for further detailed statistical analyses. Third, we measured an estimation of cognitive ability at two timepoints only; therefore precise inferences on the timing of cognitive impairment are not possible. We used an abbreviation of a full-scale intelligence test to calculate an estimation of general intellectual ability. However, these two subtests were in a previous study found to be a reasonable estimate of intelligence in the adolescent psychiatric population⁵⁹. Within this longitudinal study participants were assessed with WISC at baseline and WAIS-III at follow up and others transitioned from WAIS to WAIS-III. There is limited research on the transition from WISC to WAIS in longitudinal studies and possible effects on test scores⁶⁰. However, in previous studies transition between different versions of Wechsler scales did not affect the results⁶¹. Furthermore, our results may have been influenced by confounding factors such as experience of stress or traumatic events^{49,62} or medication use^{20,63}. Finally, a selection bias could have arisen since participants were recruited through the Dutch Association for Manic Depressives and Relatives and bipolar outpatient clinics across the country, suggesting a selection of better-informed and treatment-seeking bipolar parents.

Despite these limitations, this study is a first step in using a longitudinal design to investigate cognitive development in youth at familial risk for BD. More longitudinal studies are needed to further explore cognitive functioning during different illness phases for a better understanding of the course and mechanisms behind evolving brain-related pathology.

In summary, these findings suggest that cognitive development show a larger decline in BD offspring who develop psychopathology at a young age (≤ 16 years), as compared to offspring who develop psychopathology later in life or without psychopathology evident at early adulthood. Those offspring who develop psychopathology early in life may be at particularly high genetic liability and vulnerable to both psychiatric symptoms and cognitive impairment. Further longitudinal studies are needed to investigate the course of cognitive development in bipolar offspring and associated psychopathology.

Acknowledgement

We are grateful to the participants and family members who took part in this study.

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Appendix

Table 3. Subtests raw scores

	All participants N= 92 (%)	No disorder* N= 25	Any disorder* N= 67	Bipolar spectrum disorder N= 13	Unipolar mood disorder N= 40	Other disorder^ N= 49
Mean Vocabulary raw score at baseline	43.3 (SD 9.7)	43.5 (SD 7.1)	43.2 (SD 10.5)	46.8 (SD 10.7)	43.3 (SD 8.8)	44.0 (SD 10.5)
Mean Block Design raw score at baseline	43.5 (SD 17.1)	45.8 (SD 17.6)	42.6 (SD 17.0)	44.4 (SD 16.6)	43.7 (SD 16.0)	42.1 (SD 17.1)
Mean Vocabulary raw score at 12 year assessment	45.9 (SD 9.0)	48.6 (SD 7.7)	44.9 (SD 9.4)	47.2 (SD 11.3)	43.5 (SD 8.7)	45.5 (SD 9.6)
Mean Block Design at 12 year assessment	50.1 (SD 13.1)	53.0 (SD 11.7)	49.0 (SD 13.5)	45.1 (SD 15.9)	48.9 (SD 12.9)	49.8 (SD 12.3)

Table 4. Educational underachievement

Primary life time diagnosis	Underachievement N (%)	OR (95% CI)
No disorder	11 (50.0%)	Reference group
Any disorder	14 (51.9%)	1.26 (0.46- 3.48)
Any mood disorder	5 (62.5%)	1.27 (0.48-3.40)
Other disorder	12 (63.2%)	1.85 (0.71-4.78)

Underachievement = decline in educational level, grade retention and/or early school termination

6

Summary and General Discussion

SUMMARY

In this thesis we explored the relationship between poor educational achievement and psychopathology. Examining the association between educational achievement and mental health problems and development of psychiatric disorders is important to investigate the potential value of educational achievement as an indicator of individuals and groups at risk. Knowledge generated by such studies may increase our understanding of the etiology of psychopathology.

- One important question in the context of the relationship between poor educational achievement and psychopathology is the nature of the relationship. This is exactly what we investigated in chapter two. In this chapter we examined whether poor educational achievement reflects other risk factors or, alternatively, should be considered as a risk factor by itself. To address this question we studied a sample of well over ten thousand adolescents. In collaboration with the Public Health Centre we analysed the association of delayed school progression (grade retention) with general mental health problems measured with the Strengths and Difficulties Questionnaire (SDQ)¹ in a large cross-sectional secondary school survey comprising 10,803 adolescents. We examined the relations with socio-demographic characteristics, adverse life events, school-related factors, risk taking behaviour, healthy lifestyle and physical health. The results of our study indicated that poor educational achievement is associated with general mental health problems in adolescence. However, this relationship is heavily confounded by other factors, in particular socio-demographic factors and adverse life events. Taken together, these results suggest that poor educational achievement is not a risk factor by itself but rather a reflection of other risk factors and should be considered an indicator for mental health problems.

- In chapter three we revisited the relationship between poor educational achievement and general mental health problems. This time we shifted our focus from socio-demographic factors (chapter two) to education-related factors influencing the relationship between educational achievement and mental health problems. For this study we examined the data obtained from the next wave of the same large secondary school survey study. Poor educational achievement was here defined as a lower actual school track than expected (predicted by the teacher at the end of primary school). We again used the SDQ to measure general mental health problems. The core question of this study was the interaction between poor

educational achievement and predicted educational performance. Our results showed that poor educational achievement was associated with general mental health problems in adolescents, especially with hyperactivity symptoms, in pupils who started in high educational tracks and then decreased performance. In other words, we observed in the data that hyperactivity symptoms were prevalent in pupils who started in high educational tracks but subsequently showed a decrease in academic performance. The results confirm that poor educational achievement can be viewed as an indicator of general mental health problems, in particular when pupils originally started at higher tracks followed by a downgrading during their subsequent years in secondary school. This finding also shows that there may be differences between subgroups of underachievers in the relationship between poor educational achievement and mental health problems (depending on the tracks pupils are in).

- Next, in chapter four we set out to investigate to what extent educational achievement is affected in patients with different disorders. The central question here was to what extent educational achievement may be differentially affected by various types of psychiatric disorders. We investigated the specificity of educational achievement in data derived from a merger of psychiatric case registries and population surveys by the governmental statistics agency. In this large dataset (about 10.000 patients) we compared the highest educational achievements of patients with schizophrenia, bipolar disorder or depression and their siblings, matched with unaffected controls. The results showed that lower educational achievement was present in schizophrenia patients, from primary school onwards, compared to patients with bipolar disorder or depression. These findings confirm that specific patterns of educational achievement are associated with different psychiatric disorders.

In addition, we investigated the contribution of familial vulnerability to psychiatric disorders in educational performance. Here, we wanted to know whether there is a genetic component contributing to both poor educational achievement and development of psychiatric disorder since individuals with high genetic loading for schizophrenia (unaffected family member of schizophrenia patients) also show poorer educational achievement. The results of this study showed that siblings of schizophrenia, bipolar or depressed patients did not show educational underachievement at primary or secondary school. However, siblings of schizophrenia patients as well as siblings of depressed patients were less successful in their educational achievement after secondary school. In contrast, secondary educational achievement of siblings of bipolar patients remained without impairment over time.

Our observations show that early poor educational achievement (i.e. starting at primary school) may be specifically related to schizophrenia as this phenomenon was not observed in patients who were diagnosed with bipolar disorder or depression. Furthermore, this impairment relatively early in life appears intrinsic to suffering from the illness itself, rather than a reflection of the genetic loading of the disorder, since it is not observed in the siblings.

- The question of genetic loading is very relevant. Some of the observed symptoms may be a consequence of the disease, whereas other symptoms may be only indirectly related to the disease as they are caused by the same genetic risk factors that cause the disease. It is precisely this distinction that is the focus of chapter five. Here, we examined an estimate of cognitive achievement and educational achievement in an at-risk population of offspring of bipolar parents. Offspring of bipolar parents share the genetic burden for this disease but do not all develop the disorder themselves, even though they are at increased risk. This research was part of the prospective Dutch Bipolar Offspring Study^{2,3}, in which bipolar offspring are assessed between adolescence and adulthood on several aspects including development of psychiatric disorders and educational achievement. Poor educational achievement was here defined as a decline in educational track, grade retention and/or early school termination (without graduation).

In this study, the results suggest that cognitive development was worse in bipolar offspring who develop psychopathology at a young age (≤ 16 years), as compared to offspring who develop psychopathology later in life (and, naturally, compared to those who develop no psychopathology). This effect was not reflected in poor educational achievement.

This possible aberrant cognitive development in bipolar offspring may be a sign of underlying vulnerability for impaired neurodevelopment affecting both psychiatric symptoms and general intellectual ability or a direct illness related effect. In other words, for this particular phenomenon the findings of the study could not differentiate between the effects of the generic burden and the consequences of having the illness.

GENERAL CONCLUSION

The results from the first part of the thesis suggest that poor educational achievement at secondary school can be used as an indicator of mental health problems in adolescents. We first hypothesized that poor educational achievement would act as an independent risk factor for psychopathology but we did not find evidence that it is a risk factor by itself, instead our data indicated that poor educational achievement indexes a range of other risk factors, in particular socio-demographic factors and adverse life events. The results are consistent with a model whereby poor educational achievement acts differently in subgroups of pupils with different levels of achievement; for instance we found that it was a stronger indicator in pupils starting in higher tracks than pupils starting in lower tracks at secondary school. These findings also suggest that not the level of performance is informative, but rather the decline in education or shortfall in expected performance.

In the second part of the thesis we investigated the specificity of poor educational achievement and showed that poor educational achievement from primary school onwards is specifically related to schizophrenia and not to other psychiatric disorders we studied. In addition, this educational pattern appears to be intrinsic to the illness since it is not found in siblings. In other words, a specific relationship exists between schizophrenia and poor educational achievement compared to other major psychiatric illnesses. As such, further investigating trajectories of educational achievement can add to knowledge of aetiology of schizophrenia. Our finding that educational impairment occurs from early age onwards in schizophrenia is also interesting because it supports a neurodevelopmental model in which deficits in cognition are seen many years before illness onset.

Our results further suggest that cognitive performance is worse in bipolar offspring developing psychopathology at a young age, compared to offspring developing psychopathology later in life or no psychopathology. This finding may indicate that the offspring who develop any illness at early age are more likely to be individuals of particularly high genetic liability, with a vulnerability to both psychiatric symptoms and cognitive impairment that can progress into early adulthood.

Interestingly, in our exploration of a possible association between poor educational achievement and psychopathology in bipolar offspring, we found no relation between IQ decline and poor educational achievement, however our study was hampered by incomplete data. It is important for future research to investigate the nature of the relationship between cognitive decline and educational achievement, whether there exists a direct effect or is it influenced by other factors such as illness.

Methodological considerations

A number of methodological limitations should be taken into account by the studies presented here in this thesis. First, both waves of the large general population study described in chapters 2 and 3 had a cross-sectional design and used the self reported version of the Strengths and Difficulties Questionnaire (SDQ) as an outcome measure to identify general mental health problems. Although the SDQ gives a reliable indication of psychopathology, it is not a formal assessment of psychiatric disorders. Both assessments included a longitudinal aspect because retrospective information was obtained in the survey, but follow-up data on the pupil's educational achievement and mental health including any psychiatric disorder were not available.

In addition, delayed school progression and downgrading in tracks are crude measures of underachievement and identifies a heterogeneous group of pupils. It can be argued however that it clearly represents a "true life" indicator of underachievement. Another shortcoming is the fact that no data on pupils in special needs education was available and the results may not be generalizable to the entire population.

The study described in chapter four also had a cross-sectional, retrospective design. Crucial information was obtained from case registrars at the costs of having large amounts of missing data on educational achievement. We analysed data on completed education; therefore, precise inferences are not possible regarding the timing of underachievement. In this study special needs education was excluded as well since this type of education is organised differently and therefore hard to compare with regular education.

In chapter five we described results from a longitudinal fixed cohort study of bipolar offspring. There are few longitudinal bipolar offspring studies and research on cognitive development over time in bipolar offspring including modifying factors is even scarcer. The study had a prospective design, in contrast to the previous studies. However in this study we did not have access to an unaffected control group. Also, due to the small sample size statistical analyses of inferential type lacked power. Furthermore, cognitive ability was measured at two timepoints between adolescence and adulthood; therefore investigating cognitive development in more detail on timing was not possible.

In general, several unmeasured factors with possible effects on educational achievement and/or psychopathology such as smoking, alcohol/illicit drug use and medication were not taken into account in the studies described in this thesis. Furthermore, we used different definitions of poor educational achievement in the studies, which might hamper comparability. However, the different definitions we used, originated from real-life situations.

Clinical implications:

Our results confirm that poor educational achievement is related to mental health problems and show that it can be used as a marker for general psychopathology in adolescents. Since school-personnel are often the first to recognize poor educational achievement, workers in the educational field have an opportunity to contribute to screening, detection and intervention of mental health problems. First of all, teachers, school-doctors, school-psychologists and other school-based personnel need to be aware of the risk for psychopathology associated with poor educational achievement. Next, because we showed that poor educational achievement can be used as a (first) marker for psychopathology, pupils who underachieve are good candidates for screening for other signs of mental health problems. In particular pupils at higher levels who decline in education, since we demonstrated higher odds ratios for general psychopathology in this subgroup in chapter three. Considering that the association between mental health problems and poor educational achievement was most pronounced for hyperactivity symptoms, further attention to features of attention deficit hyperactivity disorder is warranted. Then a stepwise approach within the community health services can ensure appropriate interventions depending on severity of mental health problems. The data of this thesis give rise to further debate on the potential to systematically include educational performance data in such programmes.

Moreover, other health care workers could benefit from data on school progression as a risk marker for general psychopathology. For instance, school nurses or doctors associated with Public Health Centre can combine information on known risk factors and poor educational achievement with other relevant knowledge for instance about the social situation, to act more quickly when pupils are at risk for mental health problems.

A clinical translation of findings in chapter five, (where we show that youth at risk for mental illness based on genetic predisposition show worse cognitive functioning when they develop psychiatric disorders at early age) is that youth at risk for mental illness due to high genetic loading should be monitored closely, not only for symptoms of their parents' illness but also on the development of other psychiatric illnesses.

Finally, besides opportunities for poor educational achievement as an identifying marker for mental health problems, focussing on the improvement of educational achievement is an important goal in itself. Indeed, educational impairments are often distressing for individuals and may directly result in a lower level of education, which has life-long consequences as it contributes to low SES, low income and higher probability of unemployment⁴⁻⁶.

FINAL CONCLUSION

This thesis shows that poor educational achievement has some albeit limited value as a marker for psychosocial problems in adolescents and for groups at risk for developing severe psychopathology, in particular schizophrenia. It also shows that early onset of any psychopathology in a population at risk for bipolar disorder is associated with a worse cognitive outcome.

Since poor educational achievement is an easily available, unbiased and non-invasive marker it is worthwhile to further investigate possibilities for contribution to early identification and treatment of mental health problems including schizophrenia.

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7

Summary in Dutch
Nederlandse samenvatting

SAMENVATTING

In dit proefschrift worden verschillende studies beschreven die tot doel hebben om de relatie tussen schoolprestaties en psychopathologie in kaart te brengen. Dit is relevant om de mogelijkheid van schoolprestatie als indicator voor personen en groepen met een verhoogde kans op psychische problemen verder te onderzoeken. De kennis die door dergelijke studies wordt gegenereerd, kan ons begrip van de etiologie van psychopathologie vergroten.

In hoofdstuk 2 hebben we de aard van de relatie tussen verslechtering in schoolprestatie en psychosociaal functioneren onderzocht. Daarvoor hebben we bekeken of een verslechtering in schoolprestatie een weerspiegeling is van andere risicofactoren of als risicofactor op zichzelf moet worden beschouwd. Om deze vraag te beantwoorden hebben we gegevens uit een steekproef van ruim tienduizend adolescenten bestudeerd. Deze leerlingen van middelbare scholen in de regio Utrecht hebben een digitale vragenlijst ingevuld met betrekking tot hun psychosociaal functioneren. In samenwerking met Gemeentelijke Gezondheidsdienst (GGD) van de regio Utrecht hebben we de samenhang van onderwijsvertraging (doublure) met algemene psychische problemen geanalyseerd. We hebben de relaties onderzocht met sociaal-demografische factoren, ingrijpende tegenslagen, school gerelateerde factoren (zoals schoolveiligheid), risicovol gedrag, gezonde levensstijl en lichamelijke gezondheid. De resultaten van deze studie wijzen erop dat onderwijsvertraging geassocieerd is met algemene psychische problemen in de adolescentie. Dit verband lijkt daarbij vooral samen te hangen met andere factoren die ook van invloed zijn op psychisch functioneren, met name sociodemografische factoren (bijvoorbeeld allochtone afkomst) en tegenslagen. Dit suggereert dat onderwijsvertraging niet zozeer een op zichzelf staande risicofactor is voor psychopathologie, maar eerder een weerspiegeling van andere risicofactoren zoals sociodemografische factoren en trauma. Onderwijsvertraging kan dan worden gezien als indicator voor psychosociaal functioneren, in andere woorden, onderwijsvertraging kan erop wijzen dat er psychische problemen spelen.

In hoofdstuk 3 hebben we de relatie tussen een verminderde schoolprestatie en psychosociaal functioneren opnieuw bestudeerd. Deze keer hebben we de focus van sociaal-demografische factoren (hoofdstuk 2) verschoven naar onderwijsfactoren. Verminderde schoolprestatie werd hier gedefinieerd als 'afstroom': de situatie wanneer leerlingen in schoolniveau zakken (bijvoorbeeld van VWO naar HAVO). We gebruikten het schooladvies van de basisschool als

uitgangsniveau. In deze studie hebben we de gegevens geanalyseerd die werden verkregen uit de volgende meting van de steekproef onder adolescenten in samenwerking met de GGD regio Utrecht.

Onze resultaten lieten zien dat verslechtering in schoolprestatie geassocieerd was met algemene psychische problemen bij leerlingen die op hoger schoolniveau begonnen en vervolgens in niveau daalden. Zij rapporteerden met name symptomen van hyperactiviteit. Concluderend kan verslechtering in schoolprestatie worden gezien als indicator voor psychosociaal functioneren. Uit onze bevindingen blijkt ook dat er verschillen kunnen zijn tussen subgroepen van leerlingen (afhankelijk van de schoolniveaus) in de relatie tussen verslechtering in schoolprestatie en psychosociaal functioneren.

In hoofdstuk 4 hebben we de onderwijsvoortgang onderzocht in verschillende groepen mensen met een psychiatrische stoornis. De belangrijkste vraag hier was of de voortgang in onderwijs specifiek gerelateerd is aan een bepaalde psychiatrische stoornis. We hebben dit onderzocht in de gegevens van het Centraal Bureau voor de Statistiek (CBS) en deze gekoppeld aan gegevens van een psychiatrisch casus register. In deze dataset van ongeveer 10.000 patiënten vergeleken we het hoogst voltooide onderwijsniveau van patiënten met schizofrenie, bipolaire stoornis of depressie, en hun broers en zussen. We vergeleken dit met de onderwijsvoortgang van controles zonder deze psychiatrische stoornissen. De resultaten toonden aan dat in de groep mensen die schizofrenie ontwikkelden, er meer mensen hun basisschool niet afmaakten dan in de groep met controles. Dit werd niet geobserveerd bij mensen met een bipolaire stoornis of depressie. Deze bevindingen zijn in lijn met resultaten uit eerder onderzoek dat verslechtering in schoolprestatie specifiek gerelateerd is aan schizofrenie.

Daarnaast onderzochten we in dit hoofdstuk de bijdrage van familiale kwetsbaarheid naar psychiatrische stoornissen in onderwijsvoortgang. We bestudeerden of een genetische component bijdraagt aan zowel de voortgang in het onderwijs als de ontwikkeling van psychiatrische stoornissen. Eerder onderzoek liet namelijk zien dat mensen met een hoge genetische belasting voor schizofrenie ook een groter risico op slechtere schoolprestaties hebben. Uit de resultaten van onze studie bleek dat broers en zussen van patiënten met schizofrenie, bipolaire stoornis of depressie vergelijkbare onderwijsvoortgang hadden als de controles. Wel waren broers en zussen van patiënten met schizofrenie, en broers en zussen van patiënten met een depressie waren minder succesvol in hun schoolprestaties in het hoger onderwijs, na de middelbare school.

Deze resultaten tonen aan dat onderwijsvoortgang een specifiek verband heeft met de ontwikkeling van schizofrenie, waarbij dit niet werd aangetoond bij patiënten met een bipolaire stoornis of depressie. Bovendien lijkt het bij de ziekte schizofrenie zelf te horen, en niet aan de genetische belasting van deze aandoening, aangezien het niet in de broers en zussen van patiënten met schizofrenie werd waargenomen.

In hoofdstuk 5 zijn we verder ingegaan op de kwestie van genetische belasting. We bestudeerden een schatting van het IQ en een verslechtering in schoolprestatie in een hoog-risico populatie van nakomelingen van bipolaire ouders. Deze kinderen van ouders met een bipolaire stoornis delen de genetische last voor deze ziekte, maar ontwikkelen niet allemaal de stoornis, ondanks het verhoogde risico. Dit onderzoek was onderdeel van de Dutch Bipolar Offspring Study, waarin kinderen van ouders met een bipolaire stoornis worden onderzocht in de periode tussen adolescentie en volwassenheid op diverse elementen, zoals de ontwikkeling van psychiatrische stoornissen en cognitie. Verslechtering van schoolprestatie werd hier gedefinieerd als een doublure, afstroom en/of voortijdige schoolverlating (wanneer leerlingen hun opleiding staken zonder diploma).

De resultaten van deze studie suggereren dat de cognitieve ontwikkeling slechter is bij kinderen van ouders met een bipolaire stoornis die op jonge leeftijd (≤ 16 jaar) psychopathologie ontwikkelen, in vergelijking met de kinderen die op latere leeftijd psychopathologie ontwikkelen (en in vergelijking met kinderen die geen psychopathologie ontwikkelen). Dit effect zagen we niet optreden in verslechtering in schoolprestatie, maar er ontbraken in de studie gegevens over schoolprestaties.

Deze mogelijk afwijkende cognitieve ontwikkeling in kinderen van ouders met een bipolaire stoornis kan een teken zijn van een onderliggende kwetsbaarheid voor een verstoorde breinontwikkeling die zowel psychiatrische symptomen als algemene intellectuele vaardigheden beïnvloedt, of kan een direct effect zijn van de psychiatrische ziekte.

ALGEMENE CONCLUSIE

Samenvattend wijzen de bevindingen van het eerste deel van het proefschrift er op dat een verslechtering in schoolprestatie op de middelbare school kan worden gezien als indicator voor problemen in de psychische gezondheid bij adolescenten. Verslechtering in schoolprestatie blijkt een weerspiegeling van andere risicofactoren zoals tegenslag en sociaal-demografische factoren. Ook werd duidelijk dat er verschillen zijn in de relatie tussen schoolprestatie en psychosociaal functioneren in subgroepen van leerlingen.

In het tweede deel van het proefschrift onderzochten we de specificiteit van onderwijsvoortgang. Hierbij kwam naar voren dat dit specifiek gerelateerd is aan schizofrenie. Bovendien lijkt dit inherent aan de ziekte zelf te zijn, aangezien we het niet observeerden bij broers en zussen van patiënten met schizofrenie. Onze resultaten suggereren verder dat cognitieve prestaties slechter zijn bij kinderen van ouders met een bipolaire stoornis die op jonge leeftijd psychopathologie ontwikkelen, in vergelijking met kinderen die later in het leven psychopathologie ontwikkelen of geen psychopathologie hebben.

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Dankwoord

DANKWOORD

Als eerste wil ik mijn dank uit spreken aan alle deelnemers van de studies waar ik over heb mogen schrijven. Zij hebben de basis gelegd waarop ik mijn onderzoek heb kunnen doen.

De afgelopen jaren heb ik met veel plezier met verschillende mensen samengewerkt aan dit proefschrift en ondertussen was de hulp en steun van vele mensen onontbeerlijk. Dank daarvoor!

Beste Marco, veel dank voor je steun en vrijheid om in mijn tempo de weg te vinden in deze onderzoekswereld. Ik bewonder jouw intrinsieke gedrevenheid voor het onderzoek, naast je vakbekwaamheid als psychiater. Ik heb je begeleiding zeer gewaardeerd, je slaagt er goed in om op de juiste momenten te motiveren, steunen, kritisch of geduldig te zijn.

Beste René, dank voor het vertrouwen en het mogelijk maken van deze promotie. Ik heb veel geleerd van je feedback en visie over het onderzoek. Je adviezen over opleiding, werk of verhuizen met een gezin naar Noord-Amerika hebben me erg geholpen.

Beste Manon, dank voor je geduld en betrokkenheid. Veel dank voor de motivatie en benodigde steun in de rug aan het einde van dit traject. Het is een eer om nu bij jou als professor te kunnen promoveren.

De leden van de beoordelingscommissie, prof. dr. N. de Wit, prof. dr. W. Cahn, prof. dr. S. Durston, prof. dr. P. van Lier en prof. G. Schrijvers wil ik danken voor het kritisch lezen en beoordelen van dit manuscript.

Dank aan Niek en Alma die in het eerste uur betrokken waren bij dit promotietraject. Helaas heeft die samenwerking niet tot een succesvol project geleid maar ik heb veel geleerd van jullie adviezen.

Speciale dank en waardering gaat uit naar de medewerkers van GGD Midden-Nederland voor de fijne samenwerking: Carolien Plevier, Clothilde Bun en Nelleke de Vos.

Fabian, dank voor je heldere kijk op de statistiek, je geduldige uitleg en je motivatie voor de voortgang.

Furthermore, I would like to thank James for the wonderful research time at IoP. Working in this prestigious institute was a great experience. Mireille and Jeffrey, I really enjoyed our lunches and other meetings in London.

Willemijn, veel dank voor de gezellige samenwerking, je bijdrages aan de paper en de steun gedurende dit gehele traject. Kirstin, ook dank voor al jouw meedenken en gezellig thee/lunch-momenten. Fijn dat we elkaar ook zien buiten het werk!

Esther, dank voor de goede samenwerking, ik heb veel gehad aan je heldere, efficiënte en snelle feedback.

Stagiaires /studenten, in het bijzonder Miesje en Chris wil ik danken voor hun bijdrage aan de papers en Annemieke, Bo, Ilse en Manouk voor hun inzet bij het lesgeven op de basisscholen. Verder natuurlijk veel dank ook aan Andrea, Birgit, Eva H, Eva W, Patricia en Sarah.

Onderzoek is een heel proces en dat doe je gelukkig niet alleen, ik ben blij dat ik met anderen die zoektocht heb kunnen delen. Ik kan niet iedereen opnoemen maar ik wil sommigen in het bijzonder noemen. Deze weg ben ik gestart met: Afke, Jacobine, Kim, Metten, Monica, Paula, Renate en Sander. Dank ook aan Annabel en Lucija.

Collega arts-assistenten, onderzoekers, psychiaters en secretaresses van het UMC Utrecht wil ik graag danken voor een goede opleidings- en promotietijd. Bedankt voor alle hulp, advies en ondersteuning. In het bijzonder dank aan mijn directe supervisors Babette, Ine, Marjan, Metten, Patricia, Peter, Saskia, Tessa, Wiepke.

Speciale dank gaat uit naar mijn intervisiegenoten; Sandra, Nienke, Nathalie, Mirte, Melisse, Martha, Marieke, Kim, Jorien en Jeroen.

Carianne, Hanneke, Merel en Susan, dank voor de gezelligheid binnen de KJP.

Na mijn opleiding ben ik door collega's bij Altrecht met open armen ontvangen. Lief SAT team, lief SPOT team, collega-psychiaters en in het bijzonder Mori, Cyrina en Els, veel dank voor jullie steun en interesse zowel op professioneel als persoonlijk gebied.

Speciale dank naar mijn familie en vrienden. Zonder jullie steun had ik dit niet voor elkaar gekregen. Jullie zijn me zeer dierbaar.

Jacob en Emmanuelle, dank voor jullie onontbeerlijke steun bij de laatste loodjes. Ze wogen het zwaarst maar dankzij jullie werd het lichter. Laten we nog vaak genieten van de vele feestdagen hier, Thanksgiving was een goed begin!

Dear Rick, thank you so much. Without your help, starting in Toronto would have been so much more difficult. We felt home at your place from day one, we feel blessed to have a family friend like you.

Mirjam, hoe kan ik je ooit bedanken voor al je steun met ons leven opbouwen hier in Toronto. Je bent een geschenk uit de hemel.

Katherine, thanks for all the support, especially during the summer days in Toronto. Your interest in both my scientific progress and our family wellbeing brightened my days and I really enjoy our playdates and coffeebreaks.

Laura, thanks for all the (practical) support with finishing this thesis and your help getting us accustomed in this lovely neighbourhood.

Arjen en Carla, dank voor jullie aanmoediging en betrokkenheid.

Metten, heel veel dank voor al je hulp in de laatste fase van de afronding.

Geertje, Janneke, Maaïke en Merit; wat is het bijzonder dat we na al die jaren nog contact hebben, dank voor jullie onophoudelijke interesse.

Lieve Aafke, Jasmijn, Jisse, Joost, Lotte, Sophie en Tijmen, Stephanie, Ismay, Marilette en Linda, wat is het heerlijk om al deze tijd met jullie samen op te lopen, ik hoop dat onze wegen nog lang gezamenlijk verder gaan. Ik mis jullie hier in Canada!

Lieve Ellen en Elianne, dank voor de bijzondere vriendschap en jullie onvoorwaardelijke steun, dat helpt me overal doorheen. De life-events spaarkaart is nu vol maar een nieuwe actie is gestart voor de geraniums in het bejaardenhuis. Ik spaar ook die zegeltjes graag met jullie.

Lieve familie en schoonfamilie, dank voor al jullie steun de afgelopen jaren. Ik ben blij dat jullie er zijn!

Lieve Aagje, Jaap, Klaas, Saartje, Akpongo, Sander, Thomas en Norah, veel dank dat jullie mij zo hartelijk hebben opgenomen in de familie. Dank voor alle steun en ruimte die ik bij jullie krijg.

Lieve opa, wat bijzonder dat je hier bij bent! Tietsia, Erik, Liselotte, Tobias, Frits en Jan, dank voor jullie interesse.

Lieve Jernst en Ynske, wat ben ik blij met jullie als broer en zus en trots op jullie! Laten we nog veel mooie momenten beleven samen met Bas, Dex en Otis. Bas, veel dank voor je humor en creativiteit, in het bijzonder voor het ontwerpen van de cover voor pappa en mij. Jernst, alle respect voor jouw doorzettingsvermogen en kracht, maar val alsjeblieft nooit van je fiets. Yns, ik heb veel bewondering voor je, je bent de beste zus ever! Ik mis jullie enorm hier aan de andere kant van de wereld.

Nog eens extra: Ynske en Elianne, wat ben ik blij met jullie aan mijn zijde als paranimfen. Betere morele support kan ik niet bedenken.

Lieve pappa en mamma, zonder jullie support had ik dit nooit kunnen bereiken. Dank voor alles wat jullie zelf aan de kant zetten voor ons en nu ook voor jullie kleinkinderen. Lieve mamma, je staat altijd voor me klaar, wanneer, waar of hoe lang je steun ook nodig is. Lieve pappa, dank dat ik heb kunnen profiteren van jouw kennis, vroeger al en nu weer. Je bent een voorbeeld met je tomeloze energie en passie voor onderwijs en onderzoek.

Lieve Eline en Cato, jullie zijn nu al zo vrolijk en stralend, wat is het leven mooi met jullie samen! We houden van jullie.

Liefste, Elemi, dank voor al je liefde en onvoorwaardelijke steun, ook bij dit traject. Je zorgt voor relativering, rust en ruimte, stimuleert me om door te zetten en het beste naar boven te halen. Ik ben blij met ons leven samen en ga graag met jou de avonturen aan die op ons pad komen, ik hou van je.

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Curriculum Vitae

CURRICULUM VITAE

Wanda Tempelaar was born on February 15, 1982 in Groningen. She lived most of her childhood in Maastricht. She graduated from secondary school in 2000 at the Montessori College Maastricht. Wanda studied medicine at the University of Utrecht with internships abroad in Surinam and Tanzania. In her final year she performed research at the department of Psychiatry under supervision of Prof. Dr. W. Cahn. Wanda actively participated in several education committees during her studies and residency.

In 2009 she started her psychiatry residencies at the University Medical Center Utrecht (UMCU) under supervision of Prof Dr. R. Kahn, Dr. J. Wijkstra and Prof. Dr. F. Scheepers. In addition to clinical residencies at the UMCU she was a resident at St. Antonius Hospital and Altrecht. She combined her PhD program with her residency at the Rudolph Magnus Institute of Neurosciences under supervision of Prof. Dr. R. Kahn.

In 2015 she obtained her registration as (child) psychiatrist and started working at Altrecht Jeugd. In 2017 Wanda moved with her family to Toronto, Canada. She will start a fellowship at University Health Network and Centre for Addiction and Mental Health (CAMH) at the University of Toronto.

