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Complete List of Authors:	Wendt, Janine; University Medical Centre of the Johannes Gutenberg-University, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) Schmidt, Martina; University Medical Centre of the Johannes Gutenberg-University, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) König, Jochem; University Medical Centre of the Johannes Gutenberg-University, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) Patzlaff, Rainer; Institute for Pedagogy, Sensory and Media Ecology Huss, Michael; University Mainz, Child and Adolescent Psychiatry Urschitz , Michael; University Medical Centre of the Johannes Gutenberg-University, Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI)
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Young age at school entry and attention-deficit hyperactivity-disorder-related symptoms during primary school: Results of a prospective cohort study

Janine Wendt, Martina F Schmidt, Jochem König,

Rainer Patzlaff, Michael Huss, Michael S Urschitz

Janine Wendt, Epidemiologist, Martina F Schmidt, School Health Physician and General Practitioner, Jochem König, Biostatistician, Michael S Urschitz, Paediatrician and Epidemiologist, Division of Paediatric Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Centre of the Johannes Gutenberg-University, 55131 Mainz, Germany, Rainer Patzlaff, Pedagogue, Institute for Pedagogy, Sensory and Media Ecology, 70184 Stuttgart, Germany, Michael Huss, Child and Adolescent Psychiatrist and Clinical Psychologist, Department of Child and Adolescent Psychiatry, University Medical Centre of the Johannes Gutenberg-University; 55131 Mainz, Germany

Correspondence to: Michael S Urschitz, MD, EU-MSc, email urschitz@uni-mainz.de

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ABSTRACT

Objectives: Young age at school entry (ASE) has been related to impaired mental health in higher grades. To avoid negative health consequences of young ASE, preschool examinations and individual school entry deferral for young children are routinely performed by some school authorities. We aimed to investigate whether ASE was associated with attention-deficit hyperactivity disorder (ADHD)-related symptoms in pupils attending schools using a selective school enrolment procedure.

Design: Prospective, open cohort study with baseline assessments at school entry and two follow-ups in the 2nd and 4th grades.

Setting: Up to 128 Rudolf Steiner Schools located within Germany.

Participants: Of 3079 children providing data in the 2nd or 4th grade, 2671 (49.8% girls, mean age at baseline 6.7 years) were selected for analysis to avoid bias introduced by individuals at the edges of the ASE distribution.

Main outcome measures: ADHD-related symptoms were assessed at school entry and 2nd and 4th grades by parent- and teacher-reported versions of the Strengths and Difficulties Questionnaire.

Results: The agreement between parent- and teacher-reported symptoms was moderate (intra-class correlation: 0.60 and 0.46 in 2nd and 4th grade assessments, respectively). Regarding teacher reports, ASE was negatively associated with ADHD-related symptoms in 2nd grade (regression coefficient β=-0.68 per year, p-value=0.0005) and 4th grade (β=-0.56, p-value=0.0015). Associations remained after adjusting for potential confounders and pre-existing symptoms at baseline. Regarding parent reports, associations were markedly weaker in both grades (2nd grade: β=-0.22, p-value=0.13; 4th grade: β=-0.09, p-value=0.48).

Conclusions: Using a prospective study design and comprehensive adjustment for confounding and baseline symptoms, we confirmed prior evidence of the association between

young ASE and teacher-reported ADHD symptoms in primary school. Current school enrolment procedures may be not effective in preventing ASE-related negative health outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A prospective open cohort study including a large sample size of a homogeneous population throughout Germany
- ADHD-related symptoms were assessed in a multi-setting approach (at home and in school) using a validated instrument
- Adjustment for baseline symptoms at school entry from parent reports and other sociodemographic confounders
- The sole adjustment for parents-reported ADHD-related symptoms might have caused bias due to insufficient adjustment

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is an externalising neurodevelopmental disorder that results in inattention, impulsivity, and hyperactivity. Worldwide, approximately 63 million children and adolescents suffer from ADHD.[1] Hence, it is one of the most frequent chronic mental health condition in childhood.[2,3] It has been shown that affected children are at a higher risk for further comorbidities such as autism spectrum disorder and communication, learning, and motor disorders as well as intellectual disability and tic disorders.[4–6] Additionally, ADHD is associated with other externalising disorders such as oppositional defiant disorder and conduct disorders.[5,7]

There is evidence that the youngest children within a school class are at a disadvantage in many aspects compared to their older classmates. For example, they are less likely to be successful in sports leagues[8,9] and more likely to underperform throughout their school career.[10–13] Moreover, previous studies from various countries have shown that a relatively young age at school entry (ASE) increases the probability of having ADHD-related symptoms[14–17] or other psychopathology[18], of receiving a diagnosis of ADHD[13, 19–24], or being treated with stimulant medications.[19–28] The evidence is not consistent as other studies have not been able to demonstrate such associations.[29–32] Some authors concluded that this lack of association may be related to the school enrolment policy applied in some countries.[31] However, most studies investigated the relationship in retrospective or cross-sectional studies without adjusting for prevalent ADHD-related symptoms at school entry. This precludes causal inference, which demands a clear temporal relationship between school entry and the later evolvement of symptoms.

In Rudolf Steiner Schools, school enrolment policy is based rather on the results of a mandatory preschool examination (PSE) than on fixed cut-off dates for eligibility. The PSE evaluates school readiness as a function of individual motoric, linguistic, and cognitive skills.[33] School entry for children classified as "not ready for school" is consequently deferred, and they enter school one year later. Due to this selective enrolment procedure, Rudolf Steiner Schools have lower proportions of early (2%) and higher proportions of delayed school entries (13%) compared to public schools in Germany (6% and 5%, respectively).[34] This policy aims at outweighing the negative effects of young ASE on health and educational outcomes later in primary school.

We conducted a project which investigated the long-term associations between ASE, school readiness, and individual skill levels as well as several health and educational outcomes in German Rudolf Steiner Schools (i.e. the IPSUM project). In this article, we specifically report on the association between ASE and ADHD-related symptoms in primary school.

METHODS

Setting and Study Design

Following pre-tests since 2004 and a large pilot study in 2007 (65 schools, 2883 participants), the present population-based prospective open cohort study was started in 2008 in cooperation with the German Association of Rudolf Steiner Schools. The study protocol was reviewed and approved by the ethics committee of the federal physician chamber in Frankfurt/Main (Hesse; Germany). Written informed consent was obtained from parents/legal guardians prior to study enrolment.

The study was conducted with a two-stage recruiting process, a baseline assessment at school entry, and two follow-up assessments during grades 2 and 4. In 2007, all German Rudolf Steiner Schools were contacted and informed about the project by mail and personal phone calls. Twenty-two Rudolf Steiner Schools for children with special educational needs were excluded. Of 189 eligible schools in 2008, 88 (47%) agreed to participate. All eligible schools were contacted again in 2010 (N=193) and 2012 (N=201) and allowed to join the study. Hence, the total number of participating schools increased from 104 (54%) in 2010 to 123 (61%) in 2012.

Study Population and Sample

Study material (i.e. study information, questionnaires and consent forms) were sent to the local school enrolment committee of eligible schools. All parents who registered their child at one of the participating schools for school enrolment in 2008 were approached by the respective committee and written informed consent and the baseline questionnaire were obtained. In total 3373 children underwent the PSE, and parents of 2100 children (62%) gave consent for study participation. Children, who were ultimately not enrolled in the first grade

were later excluded from the study. In 2010, all parents of 2nd graders and in 2012, all parents of 4th graders were contacted and asked to participate in the follow-up assessments. Consequently, 1965 and 2617 children took part in the 2nd and 4th grade assessments, respectively.

Procedures and Instruments

The child's individual health status was investigated during preschool and in the 2nd and 4th grades via a package of widely used and well-validated instruments also used in the German Health Interview and Examination Survey for Children and Adolescents.[35] The parent-reported instruments covered general health, sleep problems, chronic health conditions, mental health problems, health-related quality of life, and socio-economic status. School-related behaviour, needs for special educational support, and school outcomes were investigated in the 2nd and 4th grades by teacher-reported questionnaires.

ADHD-related symptoms were investigated prior to school entry (only parent reports) and during the 2nd and 4th grades (parent and teacher reports) using German versions of the Hyperactivity-Inattention Subscale of the Strengths and Difficulties Questionnaire (SDQ).[36] The Hyperactivity-Inattention Subscale consists of 5 items and covers the areas of hyperactivity, inattention, and impulsivity. Each item is rated on 3-point Likert-type scale ranging from being not true (0), and somewhat true (1), to certainly true (2). A score is created from the sum of responses over the full range of the Subscale, yielding values between 0 and 10. A higher score thereby indicates more ADHD-related behaviour.

Restrictions, Definitions and Statistical Analysis

To avoid bias introduced by children at the tails of the ASE distribution, we only included children, who were participants in 2nd *or* 4th grade *and* were born between 30 June 2001, and

the respective federal state-specific school entry cut-off date in 2002 (30 June 2002 to 31 December 2002). This restriction allowed us to exclude children who has been deferred the year before or were too young for school entry according to legal regulations. According to this age restriction, 408 children were excluded, leaving a final analysis sample of 2671 children from 128 schools (Figure 1).

ASE was defined as the time interval (in years) between the date of birth and the first day in school. Despite the assumptions that date of birth is a random process and that associations between ASE and health outcomes are not confounded by other factors, we set up a theoretical causal model and identified the following potential confounders which have been associated with ADHD in the past: gestational age at birth, family structure, socio-economic status, and migrant background. To improve causal inference, ADHD-related symptoms at baseline (available from parent reports) were used to adjust for pre-existing symptoms already present prior to school entry. Gestational age at birth (preterm vs. term birth) and family structure (nuclear family vs. single-parent family, foster parents, or a children's home) was dichotomized. Based on the CASMIN classification (Comparative Analyses of Social Mobility in Industrial Nations), the socio-economic status of the parents was defined using information about the highest school-leaving qualification (general education) and vocational education.[37] The total CASMIN score ranged between 0.5 (still in education) to 7.0 (highest socio-economic level). A migrant background was determined by using parents' information on current nationality and country of birth. Children were classified as having a migrant background if at least one of the parents had a non-German nationality or was born outside Germany.

For the primary analysis, linear mixed-effects regression analysis with ASE as the independent variable and the Hyperactivity-Inattention Subscale score as the dependent

variable was conducted. Each child contributed up to 4 observations (parent and teacher reports from the 2nd and 4th grades). Effect estimates (β) and their standard errors (SE) were adjusted using 3 hierarchic adjustment sets (set 1: gender; set 2: set 1 plus birth status, family structure, CASMIN score, and migrant background; set 3: set 2 plus parent-reported Hyperactivity-Inattention Subscale score obtained at school entry). This combined analysis allows for unbiased estimation in the presence of missing outcome assessments due to the open cohort design under the missing at random assumption. Missing data for confounders in adjustment set 2 were rare and were accounted for by including missingness indicator variables. For adjustment set 3, a full multiple imputation procedure using the Monte Carlo Markov chain method (SAS procedure MI) was applied. The primary analysis was considered to be confirmatory; therefore, the level for type-1-error was set at 0.05.

To investigate the association between ASE and clinically-relevant ADHD-related symptoms, a secondary analysis was performed. For this, the Hyperactivity-Inattention Subscale score was dichotomised as either "no indication of ADHD" (score <6) or "indication of ADHD" (score ≥6) by applying German population-based reference values.[38] Associations with this binary outcome were investigated using marginal logistic regression analysis with generalised estimation equations by again combining assessments from teachers and parents in the 2nd and 4th grades in one analysis. For multiple imputation, we used fully conditional specification methods, thus accounting for the binary outcome scale. Odds ratios (OR) and their 95% confidence intervals (95%CI) were adjusted by the same variable sets as in the primary analysis. The secondary analysis was considered to be exploratory; p-values were calculated only for descriptive purposes.

Finally, the association between ASE and the frequency of ADHD indications adjusted for confounders was graphically investigated by plotting model-based predicted proportions

against ASE, stratified by gender, time of observation, and source of information. All statistical analyses were carried out using IBM SPSS Statistics version 22 and SAS version 9.4.

RESULTS

Of 2671 children, 1329 were girls (49.8%). Mean ASE was 6.66 years (SD: 0.31; min: 5.91; max: 7.24), with girls being three weeks younger than boys on average. On their first day at school, only 15 children (0.6%) were <6 years of age. On a descriptive basis, there was no association between ASE and the Hyperactivity-Inattention Subscale at baseline (correlation coefficient partialised for gender: r=-0.01, n=1288). Basic and demographic characteristics of study participants and the relationship with ASE are given in **Error! Reference source not found.**.

Table 1 Characteristics of participants at baseline (n=2671).

Characteristic	**N**	**%**	**Mean age/SD at school entry**
Gender			
Girls	1329	49,8	6.63/0.31
Boys	1342	50.2	6.68/0.30
Age at school entry (years)			
Less than 6.00	15	0.6	5.97/0.02
6.00 to 6.24	277	10.4	6.16/0.06
6.25 to 6.49	601	22.5	6.38/0.07
6.50 to 6.74	673	25.2	6.62/0.07
6.75 to 6.99	682	25.5	6.88/0.07
7.00 or older	423	15.8	7.09/0.06
Family structure			
Nuclear family	2022	75.7	6.65/0.31
Single-parent family, foster parents, other	632	23.7	6.66/0.30
Missing	17	0.6	6.57/0.22
CASMIN classification			
Still in education/0.5	52	1.9	6.62/0.27
1a/1.0	0	0	~
1b/1.7	4	0.1	6.64/0.33
2b/2.8	8	0.3	6.57/0.30
1c/3.0	57	2.1	6.66/0.30
2a/3.6	361	13.5	6.68/0.31
2c-gen/3.7	34	1.3	6.66/0.31

2c-voc/4.8	484	18.1	6.67/0.31
3a/6.1	419	15.7	6.67/0.30
3b/7.0	1246	46.6	6.64/0.30
Missing	6	0.2	6.74/0.18
Migrant background			
No	2185	81.8	6.66/0.31
Yes	481	18.0	6.65/0.31
Missing	5	0.2	6.72/0.19
Gestational age at birth			
Term	1299	48.6	6.66/0.30
Preterm	92	3.4	6.71/0.27
Missing	1393	48.0	6.65/0.31
Hyperactivity-Inattention Subscale score at baseline			
0	358	13.4	6.66/0.29
1	269	10.1	6.66/0.31
2	235	8.8	6.67/0.30
3	178	6.7	6.68/0.30
4	131	4.9	6.69/0.30
5	76	2.8	6.60/0.27
6	23	0.9	6.70/0.28
7	9	0.3	6.71/0.22
8	9	0.3	6.58/0.42
9	0	0.0	~
10	0	0.0	~
Missing	1383	51.8	6.65/0.31

Compared to girls, the Hyperactivity-Inattention Subscale score was higher among boys, regardless of the time of observation and source of information. Compared to parent reports, scores were also markedly higher in teacher reports, regardless of gender and time of observation. In addition, the score increased over time from baseline to the 2nd grade and to 4th grade in parent reports. This was not observed for teacher reports. The observed percent distribution of Hyperactivity-Inattention Subscale score stratified by gender, source of information, and time of observation is given in Figure 2.

In the primary analysis, ASE was negatively associated with Hyperactivity-Inattention Subscale score, regardless of time of observation and source of information (Table 2a). Per

one-year increase in ASE, the score decreased between -0.09 and -0.76 score units. The effect of ASE was higher for teacher-reported scores compared to parent-reported scores and higher in the 2nd grade compared to the 4th grade. Adjusting for confounders and baseline symptoms did not relevantly change effect sizes and ASE remained associated with the Hyperactivity-Inattention Subscale in the 2nd and 4th grades.

Table 2 a&b Association between age at school entry and ADHD-related symptoms (N=2671).

	Second grade						**Fourth grade**					
	Parent reports			**Teacher reports**			**Parent reports**			**Teacher reports**		
2a) Association between age at school entry and Hyperactivity-Inattention Subscale score (linear regression).												
Set	β	SE	p-value	β	SE	p-value	β	SE	p-value	β	SE	p-value
1)	-0.22	0.14	0.1303	-0.68	0.20	0.0005	-0.09	0.13	0.4793	-0.56	0.18	0.0015
2)	-0.24	0.14	0.0906	-0.70	0.20	0.0003	-0.10	0.13	0.4220	-0.58	0.18	0.0010
3)	-0.27	0.14	0.0648	-0.76	0.18	0.0001	-0.10	0.13	0.4253	-0.57	0.18	0.0015
2b) Association between age at school entry and indication of ADHD (logistic regression).												
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Set		lower	upper		lower	upper		lower	upper		lower	upper
1)	0.54	0.28	1.05	0.47	0.31	0.72	0.89	0.51	1.54	0.65	0.43	0.97
2)	0.52	0.26	1.03	0.46	0.30	0.72	0.91	0.52	1.61	0.64	0.42	0.96
3)	0.57	0.29	1.10	0.46	0.29	0.72	0.85	0.48	1.49	0.62	0.42	0.94

Set 1: adjusted for gender;
Set 2: adjusted for set 1 plus birth status, family form, CASMIN score, and migrant background;
Set 3: adjusted for set 2 plus parent-reported Hyperactivity-Inattention Subscale score at baseline.
Abbreviations: SE, standard error; OR, odds ratio; 95%CI, 95% confidence interval.

The frequency of ADHD indications ranged from 3.7% (girls, 2nd grade, parent reports) to 25.0% (boys, 2nd grade, teacher reports). Here as well, the frequency was higher among boys compared to girls and higher in teacher reports compared to parent reports. The gender-, time-, and source-stratified frequencies are illustrated in Figure 3.

In accordance with the primary analysis, ASE was again negatively associated with ADHD indications, regardless of the time of observation and source of information. However, the preventive effect of higher age was stronger in the 2nd grade (OR ranged from 0.46 to 0.57) compared to the 4th grade (OR ranged from 0.62 to 0.91). Again, adjustments for confounding and baseline symptoms did not alter results in a relevant manner. ORs and their corresponding 95%CI are shown in Table 2b.

DISCUSSION

In the present study, ASE was associated with teacher-reported ADHD-related symptoms in the 2nd and 4th grades. The association remained after adjusting for potential confounders and prevalent symptoms at school entry and was stronger in the 2nd grade compared to the 4th grade. In contrast, we found no clear association between ASE and parent-reported ADHD-related symptoms. The strengths of the study included the homogeneous population throughout Germany, the large sample size, the multi-setting approach with symptoms assessed at home *and* in school, the availability of baseline symptoms at school entry, and the adjustment for important confounders. To our knowledge, this is one of the few studies investigating the association in a prospective longitudinal design.

The results are consistent with previous findings from North America and Europe showing that the youngest children in class were more likely to be diagnosed and/or treated for ADHD compared to the oldest ones.[19–22, 25] An analysis of German administrative data showed that prevalences of both an ADHD diagnosis and ADHD medication were higher in children born immediately in the month before their designated school entry cut-off date (i.e. the youngest) compared to those, who were born in the month after those cut-off dates (i.e. the oldest).[24] Important limitations of most of the previous studies included the retrospective or cross-sectional study design and the lack of adjustment for potential confounders. In particular, the temporal relationship between school entry and the subsequent evolvement of new and not yet present symptoms has not been established and has hampered hitherto clear conclusions on causal inference. In this regard, this article extends existing literature. The association between ASE and ADHD-related symptoms remained after controlling for baseline symptoms; in fact, the effect estimates did not change at all. Although ADHD-related symptoms at school entry were correlated with symptoms in the 2nd and 4th grades, there was

no correlation with ASE at baseline. Hence, adjusting for baseline symptoms may not be of great importance. However, baseline symptoms were only available from parent reports and not from teacher reports, and these data were used to adjust effect estimates. In view of the moderate correlation between parent and teacher reports, the sole adjustment for parents-reported symptoms might have caused bias due to insufficient adjustment. However, in this study it was not possible to gather teacher ratings concerning ADHD-related behaviour prior to school enrolment.

We observed a moderate agreement between parent and teacher reports concerning ADHD-related symptoms. On average, the frequency of ADHD indications was two- to three-fold higher based on teacher ratings compared to parent ratings. This could be explained by either under-reporting of symptoms by parents and/or over-reporting by teachers or different symptom presentations at home vs. at school. However, teacher-perceived ADHD symptoms at school are of great importance because they are associated with poor educational outcomes in higher grades.[39] Beyond this, teachers may play a substantial role in initiating further diagnostic procedures for ADHD by advising parents to consult a paediatrician or child psychiatrist on the basis of the problematic behaviour.[19] In our study, parent and teacher reports were sufficiently correlated, which allowed for borrowing information by combining them into one model for correlated data. Although the Hyperactive-Inattention Subscale of the SDQ is a commonly used and validated instrument, we did not assess pre-existing or prevalent ADHD diagnoses or medication use for ADHD in this study. Hence, it is possible that children with a diagnosis of ADHD and an effective ameliorating treatment were misclassified as disease-free by the SDQ. However, this misclassification was non-differential (i.e. misclassification affected children of all ages in the same way) and would not explain our findings.

We studied the association between ASE and ADHD-related symptoms in a particular school setting where PSEs with a focus on developmental aspects are well established and school entry deferral as an educational intervention occurs routinely.[34] Also here, the negative health effects of ASE were not compensated for, because children at-risk for developing ADHD-related symptoms were obviously not appropriately identified and academically managed, e.g. by school entry deferral or transferring a child to special transitional programmes. In contrast, a large longitudinal study from Denmark including more than 932,032 children observed no relationship between ASE and ADHD medication. The authors concluded that this lack of association may be due to either the generally low usage of ADHD medication or the common practice of deferred school entry for young children in Denmark.[31] Hence, the effect of deferring school entry on ADHD should be extensively evaluated in the future.

The precise causal pathway between ASE and ADHD-related outcomes is unknown to date. Most of the previous findings support the immaturity hypothesis within the neurodevelopmental framework of ADHD. As age is related to developmental stage, the young and therefore less "mature" child may be unable to adequately cope with the cognitive, emotional, and social challenges following school entry. The discrepancy between this "relative immaturity" and school-related challenges may lead to stress and overtaxing, resulting in hyperactive-inattentive behaviours. Because relative immaturity is of more importance in early childhood, the effect of ASE may be more severe in countries enrolling children at a younger age.[40] Moreover, young ASE is also associated with poor school performance[10–13], which could induce additional stress for children and parents. It could be speculated that ADHD affects academic achievement, and, vice versa, that poor academic achievement affects behaviour leading to ADHD.[25] In the latter case, ADHD-related symptoms would be a temporal consequence of poor achievement. This should be targeted in

future studies on this topic. It is of high scientific relevance to identify the causal linkage between ASE and ADHD-related outcomes.

In summary, the youngest children within a school year may be at an increased risk of developing ADHD-related outcomes during primary school. There is increasing evidence that this association represents a causal relationship. The negative health effects of ASE can also be found in school settings with a high rate of delayed school entry. ASE should be considered an important factor when children are assessed for school readiness and school entry should be deferred when indicated. Instruments and indicators are now needed for the early identification of at-risk children prone to developing ADHD later in school career.

FOOTNOTES

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Contributors

MFS and RP initiated the IPSUM study, obtained approvals, and were involved in data acquisition. MSU provided specific knowledge regarding study design and survey methods and instruments. JW and JK cleaned the data and performed the statistical analyses. MFS, MSU, JK, and JW were involved in the interpretation of the results. MH was the content expert of the study. JW prepared the first draft of the manuscript. All authors critically reviewed, revised, and approved the final version.

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Competing interests

We have read and understood the BMJ policy on the declaration of interests and declare the following interests: JW, MFS, JK, RP, MSU: none. MH: reports grants and personal fees from Medice, grants and personal fees from Engelhard Arzneimittel, grants and personal fees from Shire, grants and personal fees from Novartis, personal fees from Janssen-Cilaq, during the conduct of the study; In addition, MH has a patent DE 10221839 B4 issued, and a patent US 20050131292 A1 issued.

Ethical approval

The study was approved by the ethics committee of the National Physician Chamber of Hesse, Germany.

Data sharing

No additional data available.

Transparency

JW affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

FIGURE LEGENDS

Figure 1 Selection process of participants over time.

Figure 2 Observed percent distribution of Hyperactivity-Inattention Subscale score stratified by gender, time of observation, and source of information.

The Hyperactivity-Inattention Subscale score ranges from 0 to 10, whereby "indication of ADHD" [borderline (6) and abnormal values (>6)] are indicated by yellow and red colours.

Figure 3 Frequency of predicted ADHD indication stratified by gender, time of observation, and source of information.

Predicted frequencies of ADHD indications are presented for boys and girls, entering school at six or seven years of age, living in a nuclear family, having the highest CASMIN score, and no migrant background. Vertical bars represent 95% confidence intervals.

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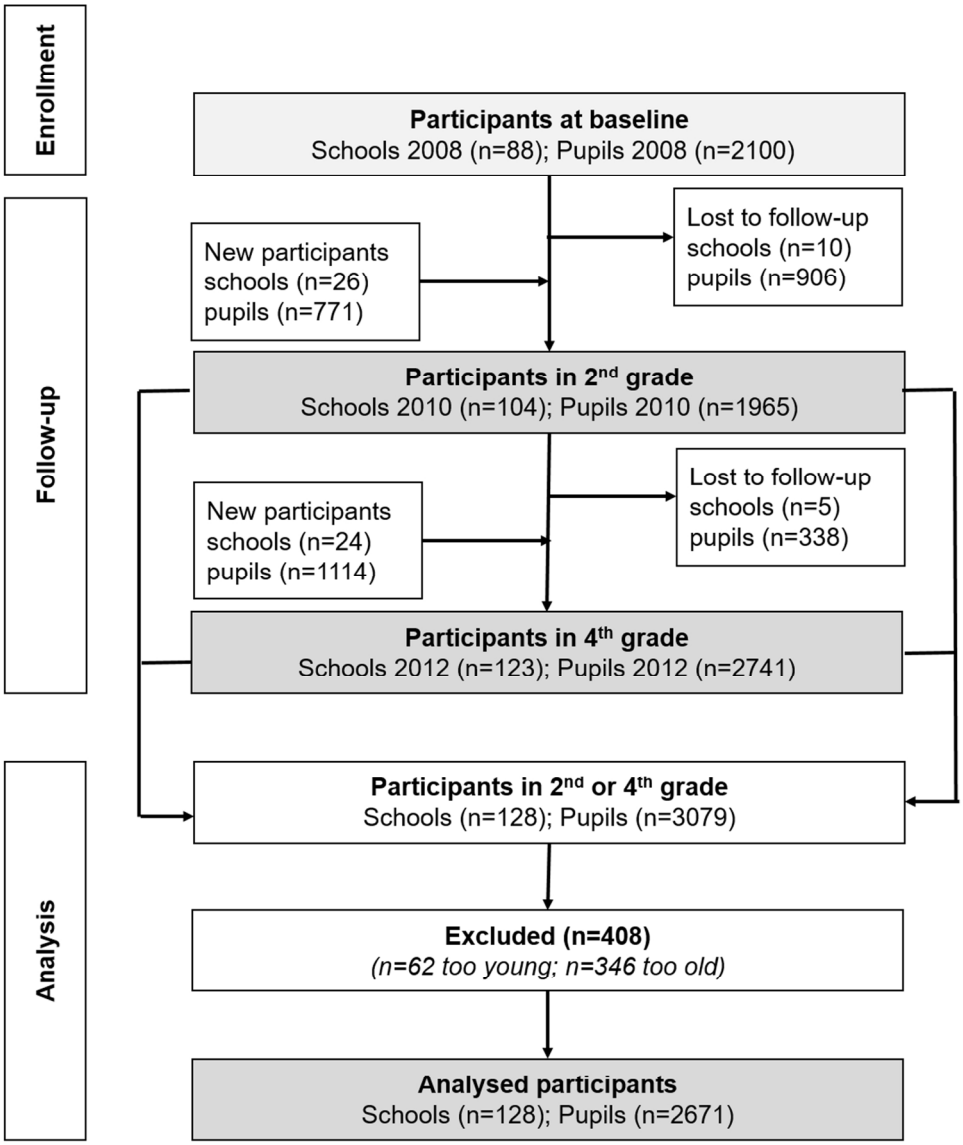

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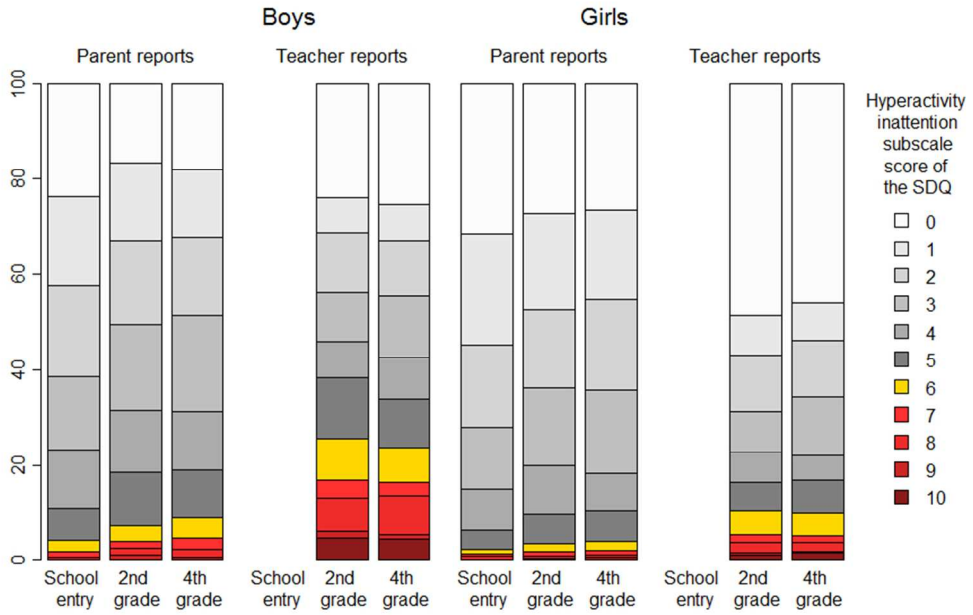

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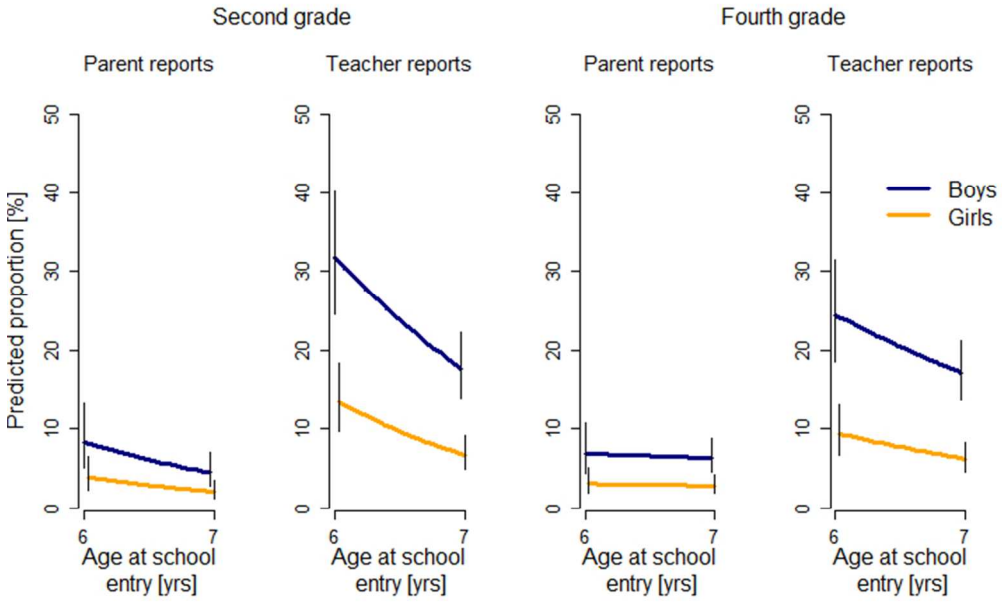

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract ✓	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale Page 5&6	2	Explain the scientific background and rationale for the investigation being reported
Objectives Page 6	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design Page 7	4	Present key elements of study design early in the paper
Setting Page 7	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants Page 7&8	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables Page 8&9	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement Page 8 to 10	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias Page 8&9	9	Describe any efforts to address potential sources of bias
Study size Page 7&8	10	Explain how the study size was arrived at
Quantitative variables Page 8 to 10	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods Page 9 to 11	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants Figure 1	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data Page 12 & 13 Table 1	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data Table 2	15*	Report numbers of outcome events or summary measures over time
Main results Page 13 & 14	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses Page 14 & 15	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results Page 16	18	Summarise key results with reference to study objectives
Limitations Page 16	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation Page 16 to 18	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability Page 18	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding Page 20	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Young age at school entry and attention deficit hyperactivity disorder related symptoms during primary school: Results of a prospective cohort study conducted at German Rudolf Steiner Schools

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Young age at school entry and attention deficit hyperactivity disorder related symptoms during primary school: Results of a prospective cohort study conducted at German Rudolf Steiner Schools

Janine Wendt[1], Martina F Schmidt[1], Jochem König[1],

Rainer Patzlaff[2], Michael Huss[3], Michael S Urschitz[1]

Janine Wendt, Epidemiologist

Martina F Schmidt, School Health Physician and General Practitioner

Jochem König, Biostatistician

Michael S Urschitz, Paediatrician and Epidemiologist

Rainer Patzlaff, Pedagogue

Michael Huss, Child and Adolescent Psychiatrist and Clinical Psychologist

1. Division of Paediatric Epidemiology, Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Centre of the Johannes Gutenberg-University, 55131 Mainz, Germany
2. Institute for Pedagogy, Sensory and Media Ecology, 70184 Stuttgart, Germany
3. Department of Child and Adolescent Psychiatry, University Medical Centre of the Johannes Gutenberg-University; 55131 Mainz, Germany

Correspondence to: Michael S Urschitz, MD, EU-MSc, email urschitz@uni-mainz.de

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ABSTRACT

Objectives: Young age at school entry (ASE) has been related to impaired mental health in higher grades. To avoid negative health consequences of young ASE, preschool examinations and individual school entry deferral for young children are routinely performed by some school authorities. We aimed to investigate whether ASE was associated with attention-deficit hyperactivity disorder (ADHD)-related symptoms in pupils attending schools using a selective school enrolment procedure.

Design: Prospective, open cohort study with baseline assessments at school entry and two follow-ups in the 2nd and 4th grades.

Setting: Up to 128 Rudolf Steiner Schools located within Germany.

Participants: Of 3079 children providing data in the 2nd or 4th grade, 2671 children born between July, 1st 2001 and October, 31st 2002 (age at baseline: mean 6.7, min 5.91, max 7.24 years, 50% girls) were selected for analysis to avoid bias introduced by individuals at the edges of the ASE distribution.

Main outcome measures: ADHD-related symptoms were assessed at school entry and 2nd and 4th grades by parent- and teacher-reported versions of the Strengths and Difficulties Questionnaire (Hyperactivity-Inattention Subscale).

Results: The agreement between parent- and teacher-reported symptoms was poor (intra-class correlation: 0.41 and 0.44 in 2nd and 4th grade assessments, respectively). Regarding teacher reports, ASE was negatively associated with ADHD-related symptoms in 2nd grade (regression coefficient β=-0.66 per year, p-value=0.0006) and 4th grade (β=-0.56, p-value=0.0014). Associations remained after adjusting for potential confounders and pre-existing symptoms at baseline. Regarding parent reports, associations were markedly weaker in both grades (2nd grade: β=-0.22, p-value=0.12; 4th grade: β=-0.09, p-value=0.48).

Conclusions: Using a prospective study design and comprehensive adjustment for confounding and baseline symptoms, we confirmed prior evidence of the association between young ASE and teacher-reported ADHD symptoms in primary school.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A prospective open cohort study including a large sample size of a homogeneous population throughout Germany
- It was possible to assess ADHD-related symptoms in a dual-setting approach (at home and in school) using a validated instrument
- We were able to adjust for baseline symptoms at school entry from parent reports and other sociodemographic confounders
- Adjusting for parent-reports of ADHD-related symptoms prior to school entry might not have been a sufficient control for analyses involving teacher reports of ADHD-related symptoms at subsequent time points.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is an externalising neurodevelopmental disorder that results in inattention, impulsivity, and hyperactivity. Worldwide, approximately 63 million children and adolescents suffer from ADHD.[1] In school-aged children the estimated prevalence of ADHD is 5 to 7%.[2–4] Hence, it is one of the most frequent chronic mental health condition in childhood.[5, 6] There is no specific single cause for ADHS, however, gender, socio-economic status, migrant background and family form are potential risk factors.[7] It has been shown that affected children are at a higher risk for further comorbidities such as autism spectrum disorder and communication, learning, and motor disorders as well as intellectual disability and tic disorders.[8–10] Additionally, ADHD is associated with other externalising disorders such as oppositional defiant disorder and conduct disorders.[9, 11]

There is evidence that the youngest children within a school class are at a disadvantage in many aspects compared to their older classmates. For example, they are less likely to be successful in sports leagues[12,13] and more likely to underperform throughout their school career.[14–17] Moreover, previous studies from various countries have shown that a relatively young age at school entry (ASE) increases the probability of having ADHD-related symptoms[18–21] or other psychopathology[22], of receiving a diagnosis of ADHD[17, 23–28], or being treated with stimulant medications.[23–32] The evidence is not consistent as other studies have not been able to demonstrate such associations.[33–36] Some authors concluded that this lack of association may be related to the school enrolment policy applied in some countries.[35] However, most studies investigated the relationship in retrospective or cross-sectional studies without adjusting for prevalent ADHD-related symptoms at school entry and other important ADHD risk factors. This may impede causal inference, which demands a clear temporal relationship between school entry and the later evolvement of symptoms.

We conducted a project which investigated the long-term associations between ASE, school readiness, and individual skill levels as well as several health and educational outcomes in German Rudolf Steiner Schools (i.e. the IPSUM project). Based on this project, we conducted a study to investigate the association between ASE and ADHD-related symptoms in primary school children. We hypothesized that children who are young for their grade have more ADHD-related symptoms compared to their older classmates.

METHODS

Setting and Study Design

Following pre-tests since 2004 and a large pilot study in 2007 (65 schools, 2883 participants), the present population-based prospective open cohort study was started in 2008 in cooperation with the German Association of Rudolf Steiner Schools. The study protocol was reviewed and approved by the ethics committee of the federal physician chamber in Frankfurt/Main (Hesse; Germany). Written informed consent was obtained from parents/legal guardians prior to study enrolment.

The study was conducted with a two-stage recruiting process, a baseline assessment at school entry (current age: 6-7 years), and two follow-up assessments during grade 2 (current age: 7-8 years) and 4 (current age: 9-10 years). In 2007, all German Rudolf Steiner Schools were contacted and informed about the project by mail and personal phone calls. Twenty-two Rudolf Steiner Schools for children with special educational needs were excluded. Of 189 eligible schools in 2008, 88 (47%) agreed to participate. All eligible schools were contacted again in 2010 (N=193) and 2012 (N=201) and allowed to join the study. Hence, the total number of participating schools increased from 104 (54%) in 2010 to 123 (61%) in 2012.

Preschool Examination and School Enrolment Policy

In Rudolf Steiner Schools, school enrolment policy is based rather on the results of a mandatory preschool examination (PSE) than on fixed cut-off dates for eligibility. The PSE evaluates school readiness as a function of individual motoric, linguistic, and cognitive skills.[37] School entry for children classified as “not ready for school” is consequently deferred, and they enter school one year later. Due to this selective enrolment procedure,

Rudolf Steiner Schools have lower proportions of early (2%) and higher proportions of delayed school entries (13%) compared to public schools in Germany (6% and 5%, respectively).[38] This policy aims at outweighing the negative effects of young ASE on health and educational outcomes later in primary school.

Study Population and Sample

Study material (i.e. study information, questionnaires and consent forms) were sent to the local school enrolment committee of eligible schools. All parents who registered their child at one of the participating schools for school enrolment in 2008 were approached by the respective committee and written informed consent and the baseline questionnaire were obtained. In total 3373 children underwent the PSE, and parents of 2100 children (62%) gave consent for study participation. Children, who were ultimately not enrolled in the first grade were later excluded from the study. In 2010, all parents of 2nd graders and in 2012, all parents of 4th graders were contacted and asked to participate in the follow-up assessments. Consequently, 1965 and 2617 children took part in the 2nd and 4th grade assessments, respectively.

Procedures and Instruments

The child's individual health status was investigated during preschool and in the 2nd and 4th grades via a package of widely used and well-validated instruments also used in the German Health Interview and Examination Survey for Children and Adolescents.[39] The parent-reported instruments covered general health, sleep problems, chronic health conditions, mental health problems, health-related quality of life, and socio-economic status. School-related behaviour, needs for special educational support, and school outcomes were investigated in the 2nd and 4th grades by teacher-reported questionnaires.

ADHD-related symptoms were investigated prior to school entry (only parent reports) and during the 2nd and 4th grades (parent and teacher reports) using German versions of the Hyperactivity-Inattention Subscale of the Strengths and Difficulties Questionnaire (SDQ).[40] The Hyperactivity-Inattention Subscale consists of 5 items and covers the areas of hyperactivity, inattention, and impulsivity. Each item is rated on 3-point Likert-type scale ranging from being not true (0), and somewhat true (1), to certainly true (2). A score is created from the sum of responses over the full range of the Subscale, yielding values between 0 and 10. A higher score thereby indicates more ADHD-related behaviour.

Restrictions, Definitions and Statistical Analysis

To avoid bias introduced by children at the tails of the ASE distribution, we only included children, who were participants in 2nd *or* 4th grade *and* were born according to Rudolf Steiner Schools cut-off date (30 June 2002) *or* the respective 2008 federal state-specific cut-off dates (30 June 2002 to 31 December 2002 depending on the state). This restriction allowed us to exclude children who has been deferred the year before or were too young for school entry according to legal regulations. According to this age restriction, 408 children were excluded (85% were too old), leaving a final analysis sample of 2671 children from 128 schools (Figure 1).

ASE was defined as the time interval (in years) between the date of birth and the first day in school. As summer holidays differ between German federal states, first day in school was individually calculated for each child. Despite the assumptions that date of birth is a random process and that associations between ASE and health outcomes are not confounded by other factors, we set up a theoretical causal model and identified the following potential confounders which have been associated with ADHD in the past[7]: gestational age at birth, family structure, socio-economic status, and migrant background. To improve causal

inference, ADHD-related symptoms at baseline (available from parent reports) were used to adjust for pre-existing symptoms already present prior to school entry. Gestational age at birth (preterm vs. term birth) and family structure (nuclear family vs. single-parent family, foster parents, or a children's home) was dichotomized. Based on the CASMIN classification (Comparative Analyses of Social Mobility in Industrial Nations), the socio-economic status of the parents was defined using information about the highest school-leaving qualification (general education) and vocational education.[41] The total CASMIN score ranged between 0.5 (still in education) to 7.0 (highest socio-economic level). A migrant background was determined by using parents' information on current nationality and country of birth. Based on the definition of the German Federal Ministry of Justice and Consumer Protection, children were classified as having a migrant background if at least one of the parents had a non-German nationality or was born outside Germany.

Cronbach's alpha and intra-class correlation coefficients were calculated to assess internal consistency of the Hyperactivity-Inattention Subscale and the agreement between parent- and teacher-reports. We used the intra-class correlations coefficient for absolute agreement of single measurements based on a model with fixed rater and random subject effect. For the primary analysis, a multivariable linear regression analysis for correlated data with ASE as the independent variable and the Hyperactivity-Inattention Subscale score as the dependent variable was conducted. Each child contributed up to 4 observations (parent and teacher reports from the 2nd and 4th grades). Effect estimates (β) and their standard errors (SE) were adjusted using 3 hierarchic adjustment sets (set 1: gender; set 2: set 1 plus birth status, family structure, CASMIN score, and migrant background; set 3: set 2 plus parent-reported Hyperactivity-Inattention Subscale score obtained at school entry). This combined analysis allows for unbiased estimation in the presence of missing outcome assessments due to the open cohort design under the missing at random assumption. Missing data for confounders in

adjustment set 2 were rare and were accounted for by including missingness indicator variables. For adjustment set 3, a full multiple imputation procedure using the Monte Carlo Markov chain method (SAS procedure MI) was applied. The primary analysis was considered to be confirmatory; therefore, the level for type-1-error was set at 0.05.

To investigate the association between ASE and clinically-relevant ADHD-related symptoms, a secondary analysis was performed. For this, the Hyperactivity-Inattention Subscale score was dichotomised as either "no indication of ADHD" (score <6) or "indication of ADHD" (score ≥6) by applying German population-based reference values.[42] Associations with this binary outcome were investigated using marginal logistic regression analysis with generalised estimation equations by again combining assessments from teachers and parents in the 2nd and 4th grades in one analysis. For multiple imputation, we used fully conditional specification methods, thus accounting for the binary outcome scale. Odds ratios (OR) and their 95% confidence intervals (95%CI) were adjusted by the same variable sets as in the primary analysis. The secondary analysis was considered to be exploratory; p-values were calculated only for descriptive purposes.

Finally, the association between ASE and the frequency of ADHD indications adjusted for confounders was graphically investigated by plotting model-based predicted proportions against ASE, stratified by gender, time of observation, and source of information. All statistical analyses were carried out using IBM SPSS Statistics version 22 and SAS version 9.4.

Sensitivity Analysis

A sensitivity analysis was carried out to examine the robustness of study findings with an alternative restriction criterion. Therefore, the sample was restricted to children, who fully

comply with the federal state-specific cut-off dates for school eligibility in 2008 (30 June 2002 to 31 December 2002 depending on state). Due to this restriction, 747 children were excluded (92% were too old), leaving a sample of 2332 children from 128 schools.

Patient and Public Involvement

Neither patients nor patient advisors have been involved in the design, the recruitment to, or the conduct of the study. However, results will be disseminated to headmasters, school health physicians, and parents of children attending German Rudolf Steiner Schools. Results will be also used to adapt and improve the preschool health examination at Rudolf Steiner Schools.

RESULTS

Of 2671 children, 1329 were girls (49.8%). The children had been born between July, 1st 2001 and October, 31st 2002. Mean ASE was 6.66 years (SD: 0.31; min: 5.91; max: 7.24), with girls being three weeks younger than boys on average. On their first day at school, only 15 children (0.6%) were <6 years of age. On a descriptive basis, there was no association between ASE and the Hyperactivity-Inattention Subscale at baseline (correlation coefficient partialised for gender: r=-0.01, n=1288). Basic and demographic characteristics of study participants and the relationship with ASE are given in Table 1.

Table 1. Characteristics of participants at baseline (n=2671).

Characteristic	**N**	**%**	**Mean age/SD at school entry**
Gender			
Girls	1329	49.8	6.63/0.31
Boys	1342	50.2	6.68/0.30
Age at school entry (years)			
Less than 6.00	15	0.6	5.97/0.02
6.00 to 6.24	277	10.4	6.16/0.06
6.25 to 6.49	601	22.5	6.38/0.07
6.50 to 6.74	673	25.2	6.62/0.07
6.75 to 6.99	682	25.5	6.88/0.07
7.00 or older	423	15.8	7.09/0.06
Family structure			
Nuclear family	2022	75.7	6.65/0.31
Single-parent family, foster parents, other	632	23.7	6.66/0.30
Missing	17	0.6	6.57/0.22
CASMIN classification			
Still in education/0.5	52	1.9	6.62/0.27
1a/1.0	0	0	~
1b/1.7	4	0.1	6.64/0.33
2b/2.8	8	0.3	6.57/0.30
1c/3.0	57	2.1	6.66/0.30
2a/3.6	361	13.5	6.68/0.31
2c-gen/3.7	34	1.3	6.66/0.31

2c-voc/4.8	484	18.1	6.67/0.31
3a/6.1	419	15.7	6.67/0.30
3b/7.0	1246	46.6	6.64/0.30
Missing	6	0.2	6.74/0.18
Migrant background			
No	2185	81.8	6.66/0.31
Yes	481	18.0	6.65/0.31
Missing	5	0.2	6.72/0.19
Gestational age at birth			
Term	1299	48.6	6.66/0.30
Preterm	92	3.4	6.71/0.27
Missing*	1393	48.0	6.65/0.31
Hyperactivity-Inattention Subscale score at baseline			
0	358	13.4	6.66/0.29
1	269	10.1	6.66/0.31
2	235	8.8	6.67/0.30
3	178	6.7	6.68/0.30
4	131	4.9	6.69/0.30
5	76	2.8	6.60/0.27
6	23	0.9	6.70/0.28
7	9	0.3	6.71/0.22
8	9	0.3	6.58/0.42
9	0	0.0	~
10	0	0.0	~
Missing*	1383	51.8	6.65/0.31

* Due to the open cohort study design the parental questionnaire at baseline was available for 1309 children only, resulting in 1362 missing values.

On a descriptive basis and compared to girls, the Hyperactivity-Inattention Subscale score was higher among boys, regardless of the time of observation and source of information. Compared to parent reports, scores were also markedly higher in teacher reports, regardless of gender and time of observation. In addition, the score increased over time from baseline to the 2nd grade and to 4th grade in parent reports. This was not observed for teacher reports. The observed percent distribution of Hyperactivity-Inattention Subscale score stratified by gender, source of information, and time of observation is given in Figure 2. Concerning the Hyperactivity-Inattention Subscale, Cronbach's alpha was 0.72, 0.75, 0.87, 0.76, and 0.87, at baseline, at 2nd grade parent and teacher reports, and at 4th grade parent and teacher reports,

respectively. The intra-class correlation between parent and teacher reports was 0.41 and 0.44 in 2nd and 4th grade, respectively.

In the primary analysis, ASE was negatively associated with Hyperactivity-Inattention Subscale score, regardless of time of observation and source of information (Table 2). Per one-year increase in ASE, the score decreased between -0.09 and -0.73 score units. On a descriptive basis, the effect of ASE was higher for teacher-reported scores compared to parent-reported scores and higher in the 2nd grade compared to the 4th grade. However, the effect of ASE for parent-reported scores did not reach statistical significance. Adjusting for confounders and baseline symptoms did not relevantly change effect sizes and ASE remained associated with the teacher-reported scores in the 2nd and 4th grades. Differences in effect sizes for parent-reported scores and teacher-reported scores between 2nd and 4th grades were not significant.

Table 2. Association between age at school entry and Hyperactivity-Inattention Subscale score (multivariable linear regression for correlated outcomes; N=2671).

Hyperactivity-Inattention Subscale score derived from the Strengths and Difficulties Questionnaire												
	Second grade						Fourth grade					
	Parent reports			Teacher reports			Parent reports			Teacher reports		
Set	β	SE	p-value	β	SE	p-value	β	SE	p-value	β	SE	p-value
1)	-0.22	0.14	0.1245	-0.66	0.19	0.0006	-0.09	0.13	0.4847	-0.56	0.17	0.0014
2)	-0.24	0.14	0.0874	-0.68	0.19	0.0004	-0.10	0.13	0.4251	-0.58	0.17	0.0009
3)	-0.27	0.14	0.0662	-0.73	0.18	0.0001	-0.10	0.13	0.4103	-0.57	0.17	0.0013

Set 1: adjusted for gender;
Set 2: adjusted for set 1 plus birth status, family form, CASMIN score, and migrant background;
Set 3: adjusted for set 2 plus parent-reported Hyperactivity-Inattention Subscale score at baseline.
Abbreviations: SE, standard error.

The frequency of ADHD indications ranged from 3.7% (girls, 2nd grade, parent reports) to 25.0% (boys, 2nd grade, teacher reports). Here as well, the frequency was higher among boys compared to girls and higher in teacher reports compared to parent reports. The gender-, time-, and source-stratified model-based predicted proportions for all ages between 6 and 7 years are illustrated in Figure 3.

In accordance with the primary analysis, ASE was again negatively associated with ADHD indications, regardless of the time of observation and source of information. On a descriptive basis, the preventive effect of higher age was stronger in the 2nd grade (OR ranged from 0.49 to 0.54) compared to the 4th grade (OR ranged from 0.59 to 0.91). Again, adjustments for confounding and baseline symptoms did not alter results in a relevant manner. ORs and their corresponding 95%CI are shown in Table 3.

Table 3 Association between age at school entry and indication of ADHD (multivariable logistic regression; N=2671).

Indication of ADHD derived from the Hyperactivity-Inattention Subscale of the Strengths and Difficulties Questionnaire												
	Second grade						Fourth grade					
	Parent reports			Teacher reports			Parent reports			Teacher reports		
		95% CI			95% CI			95% CI			95% CI	
Set	OR*	lower	upper	OR*	lower	upper	OR*	lower	upper	OR*	lower	upper
1)	0.54	0.28	1.05	0.52	0.33	0.80	0.89	0.51	1.54	0.62	0.41	0.93
2)	0.52	0.27	1.03	0.51	0.33	0.80	0.91	0.52	1.60	0.61	0.40	0.92
3)	0.50	0.24	1.04	0.49	0.30	0.81	0.83	0.47	1.47	0.59	0.39	0.89

Set 1: adjusted for gender;
Set 2: adjusted for set 1 plus birth status, family form, CASMIN score, and migrant background;
Set 3: adjusted for set 2 plus Hyperactivity-Inattention Subscale score at baseline.
Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval.
* Odds ratios are unit odds ratios per one year of ASE.

Sensitivity Analysis

In the sensitivity analysis, ASE was negatively associated with Hyperactivity-Inattention Subscale score, too, regardless of time of observation and source of information. Per one-year increase in ASE, the score decreased between 0.17 and 0.98 score units. Like in the primary analysis, the effect of ASE was higher for teacher-reported scores compared to parent-reported scores and higher in the 2nd grade compared to the 4th grade. The effect of ASE on teacher-reported scores remained significant. The adjustment for parent-reported ADHD-related symptoms at baseline (set 3) yielded a significant estimate for parent-reports in 2nd grade but not in 4th grade. Overall, the alternative restriction criterion did not change the results considerably. All results are given in the supplementary Table 1.

DISCUSSION

In the present study, ASE was associated with teacher-reported ADHD-related symptoms in the 2nd and 4th grades. The association remained after adjusting for potential confounders and prevalent symptoms at school entry and was stronger in the 2nd grade compared to the 4th grade. In contrast, we found no clear association between ASE and parent-reported ADHD-related symptoms. The strengths of the study included the homogeneous population throughout Germany, the large sample size, the dual-setting approach with symptoms assessed at home *and* in school, the availability of baseline symptoms at school entry, and the adjustment for important confounders. However, due to particularities of the setting, results should not be generalized to other settings or countries. To our knowledge, this is one of the few studies investigating the association in a prospective longitudinal design.

The results are consistent with previous findings from North America and Europe showing that the youngest children in class were more likely to be diagnosed and/or treated for ADHD compared to the oldest ones.[23–26, 29] An analysis of German administrative data showed that prevalences of both an ADHD diagnosis and ADHD medication were higher in children born immediately in the month before their designated school entry cut-off date (i.e. the youngest) compared to those, who were born in the month after those cut-off dates (i.e. the oldest).[28]

In the present study, the proportion of children with ADHD indication was very high, given that in German administrative data roughly 5% of boys in 2nd grade and 7.5% in 4th grade receive ADHD diagnoses.[28] Similarly, the prevalence of an ADHD diagnosis in boys aged 7-10 reported by parents in a German representative survey was 7.3% in 2009-2012.[43] If pupils of Rudolf Steiner Schools tend to exhibit more ADHD symptoms than the general population

the results of the present study may be only carefully generalized to the entire German population.

The prospective longitudinal design of our study allowed us to adjust for differences in ADHD-related symptoms prior to school entry which can be seen as an additional contribution to the pre-existing literature. However, it is unclear whether the longitudinal design offers methodological benefits in this specific research question. Some previous cross-sectional studies use timing of birth in narrow windows around school entry cut-off dates, which corresponds to a "natural experiment" generating variation in age for grade. There is no obvious reason to expect differences in ADHD-related symptoms before school entry across age groups, making it probably unnecessary to adjust for these differences (or other potential confounders) as there should be none. However, we decided to empirically investigate the existence of differences across age groups rather than just to argue that differences should not exist. In the present study, the association between ASE and ADHD-related symptoms remained after controlling for baseline symptoms; in fact, the effect estimates did not change at all. Although ADHD-related symptoms at school entry were correlated with symptoms in the 2nd and 4th grades, there was no correlation with ASE at baseline. Thus, adjusting for baseline symptoms may not be of great importance in such studies. On the other hand, baseline symptoms were only available from parent reports and not from teacher reports (and these data were used to adjust effect estimates) and were missing and imputed for more than half of the sample. In view of the poor agreement between parent and teacher reports, the sole adjustment for parents-reported symptoms might have caused bias due to insufficient adjustment. Nevertheless, it was not possible to gather teacher ratings concerning ADHD-related behaviour prior to school enrolment.

We observed a poor agreement between parent and teacher reports concerning ADHD-related symptoms. On average, the frequency of ADHD indications was two- to three-fold higher based on teacher ratings compared to parent ratings. This could be explained by either under-reporting of symptoms by parents and/or over-reporting by teachers or different symptom presentations at home vs. at school. However, teacher-perceived ADHD symptoms at school are of great importance because they are associated with poor educational outcomes in higher grades.[44] Beyond this, teachers may play a substantial role in initiating further diagnostic procedures for ADHD by advising parents to consult a paediatrician or child psychiatrist on the basis of the problematic behaviour.[23]

In contrast to agreement, parent and teacher reports were sufficiently correlated, which allowed for borrowing information by combining them into one model for correlated data. In general, the SDQ is a commonly used and validated screening instrument and a valid tool for discriminating cases with ADHD from those without ADHD.[45] However, in the light of that appr. 25% of boys in 2nd grade were above cut-off, the SDQ may pick up other – not strictly ADHD-related – symptoms like stress or poor adaptation to school challenges. Moreover, we did not assess pre-existing or prevalent ADHD diagnoses or medication use for ADHD in this study. Hence, it is possible that children with a diagnosis of ADHD and an effective ameliorating treatment were misclassified as disease-free by the SDQ. However, this misclassification was non-differential (i.e. misclassification affected children of all ages in the same way) and would not explain our findings. In fact, the association between ASE and ADHD diagnoses and/or medication has been already investigated by others and was not the primary aim of the present study.

We studied the association between ASE and ADHD-related symptoms in a particular school setting where PSEs with a focus on developmental aspects are well established and school

entry deferral as an educational intervention occurs routinely.[38] Also here, the negative health effects of young ASE were obviously not fully compensated for, because children at-risk for developing ADHD-related symptoms may be not sufficiently identified and appropriately managed, e.g. by school entry deferral or transferring a child to special transitional programmes. On the other hand, it is possible that the associations of ASE and ADHD-related symptoms would be even higher if there was not a preceding PSE with a focus on developmental aspects. In contrast to our results, a large longitudinal study from Denmark including more than 932,032 children observed no relationship between ASE and ADHD medication. The authors concluded that this lack of association may be due to either the generally low usage of ADHD medication or the common practice of deferred school entry for young children in Denmark.[35] Hence, the effect of deferring school entry and other educational interventions on ADHD should be extensively evaluated in the future and comparisons between different school settings should be performed.

As mentioned before, Rudolf Steiner Schools have lower proportions of early and higher proportions of delayed school entries compared to public schools in Germany. This policy truncates the age range and reduced the fraction of "very young" children in the source population of our sample. In contrast, our restriction aims at reducing the fraction of "very old" children (following school entry deferral the year bevor), because these children have serious medical and/or educational reasons for the deferral and would have introduced bias if not excluded. Based on these particularities, we performed a sensitivity analysis with a more rigorous restriction, now excluding more children at the edges of the age distribution. However, this did not change the results of the study. Although, we increased the participation proportion of schools from 47% in 2008 to 61% in 2012, we cannot warrant representativeness of the sample. Because characteristics of non-responding schools and non-responding children were not available, a corresponding analysis for representativeness was

not possible. Notwithstanding this concern, we assume that bias by self-selection was unlikely, because schools and parents were not informed about the present research question.

The precise causal pathway between ASE and ADHD-related outcomes is unknown to date. Most of the previous findings support the immaturity hypothesis within the neurodevelopmental framework of ADHD. As age is related to developmental stage, the young and therefore less "mature" child may be unable to adequately cope with the cognitive, emotional, and social challenges following school entry. The discrepancy between this "relative immaturity" and school-related challenges may lead to stress and overtaxing, resulting in hyperactive-inattentive behaviours. Because relative immaturity is of more importance in early childhood, the effect of ASE may be more severe in countries enrolling children at a younger age.[46] Moreover, young ASE is also associated with poor school performance[14–17], which could induce additional stress for children and parents. It could be speculated that ADHD affects academic achievement, and, vice versa, that poor academic achievement affects behaviour leading to ADHD.[29] In the latter case, ADHD-related symptoms would be a temporal consequence of poor achievement. This should be targeted in future studies on this topic. It is also possible that children who are young for their grade behave adequately for their age. Only when compared to their older classmates, their behaviour appears more hyperactive or impulsive and they thus receive higher ratings of ADHD-related symptoms – particularly when assessed by their teachers. As teachers are more prone to compare children within a grade than parents, this interpretation is also supported by the different findings comparing teacher and parent reports in the present and a previous US study.[23] Overall, it is of high scientific relevance to identify the causal linkage between ASE and ADHD-related outcomes.

In summary, the youngest children within a school year are at an increased risk of developing ADHD-related outcomes during primary school. There is increasing evidence that this association represents a causal relationship. The negative health effects of ASE can also be found in school settings with a high rate of delayed school entry. ASE should be considered an important factor when children are assessed for school readiness and school entry should be deferred when indicated. Instruments and indicators are now needed for the early identification of at-risk children prone to developing ADHD later in school career.

FOOTNOTES

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Contributors

MFS and RP initiated the IPSUM study, obtained approvals, and were involved in data acquisition. MSU provided specific knowledge regarding study design and survey methods and instruments. JW and JK cleaned the data and performed the statistical analyses. MFS, MSU, JK, and JW were involved in the interpretation of the results. MH was the content expert of the study. JW prepared the first draft of the manuscript. All authors critically reviewed, revised, and approved the final version.

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Competing interests

We have read and understood the BMJ policy on the declaration of interests and declare the following interests: JW, MFS, JK, RP, MSU: none. MH: reports grants and personal fees from Medice, grants and personal fees from Engelhard Arzneimittel, grants and personal fees from Shire, grants and personal fees from Novartis, personal fees from Janssen-Cilaq, during the conduct of the study; In addition, MH has a patent DE 10221839 B4 issued, and a patent US 20050131292 A1 issued.

Ethical approval

The study was approved by the ethics committee of the National Physician Chamber of Hesse, Germany.

Data sharing

No additional data available.

Transparency

JW affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

FIGURE LEGENDS

Figure 1 Selection process of participants over time.

Figure 2 Observed percent distribution of Hyperactivity-Inattention Subscale score stratified by gender, time of observation, and source of information.

The Hyperactivity-Inattention Subscale score ranges from 0 to 10, whereby "indication of ADHD" [borderline (6) and abnormal values (>6)] are indicated by yellow and red colours.

Figure 3 Frequency of predicted ADHD indication stratified by gender, time of observation, and source of information.

Predicted frequencies of ADHD indications are presented for boys and girls, entering school at six or seven years of age, living in a nuclear family, having the highest CASMIN score, and no migrant background. Vertical bars represent 95% confidence intervals.

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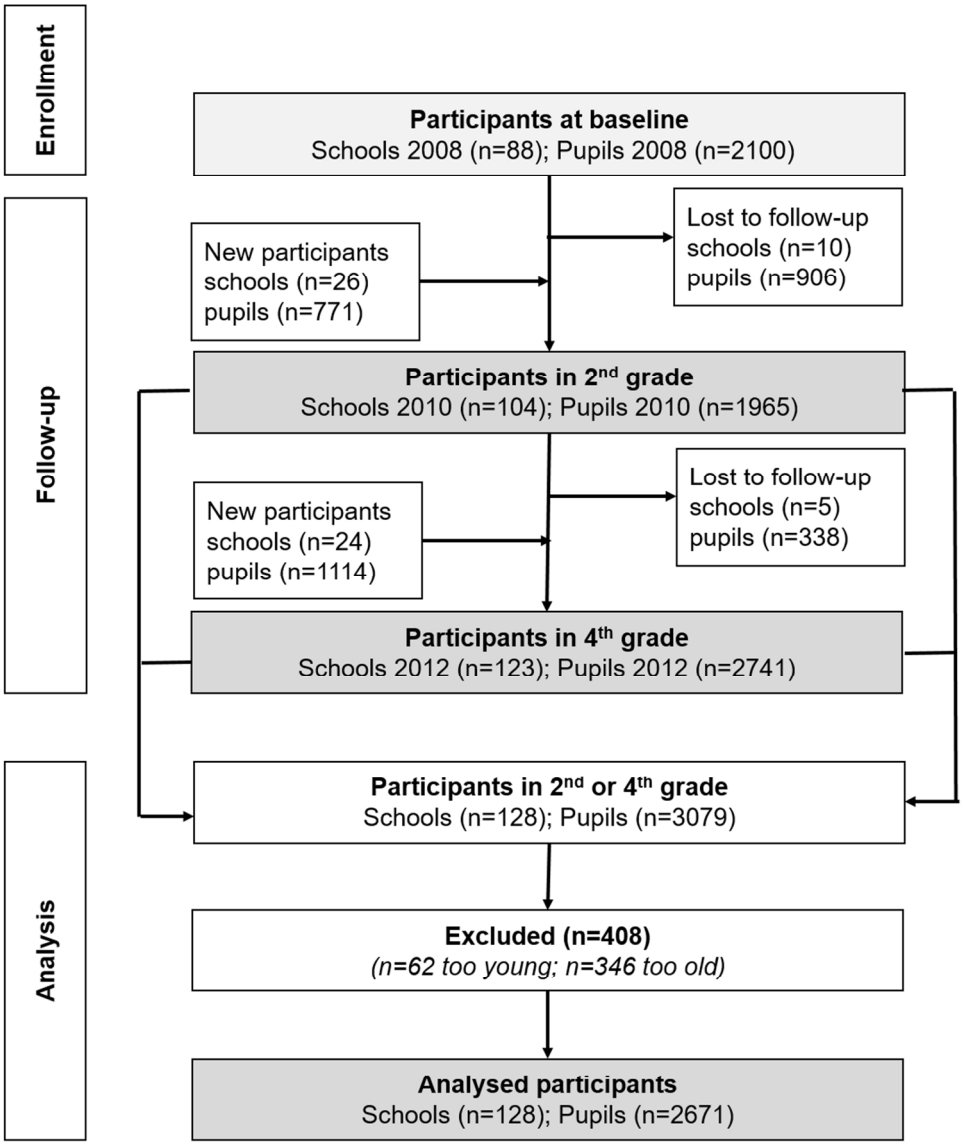

Figure 1 Selection process of participants over time.

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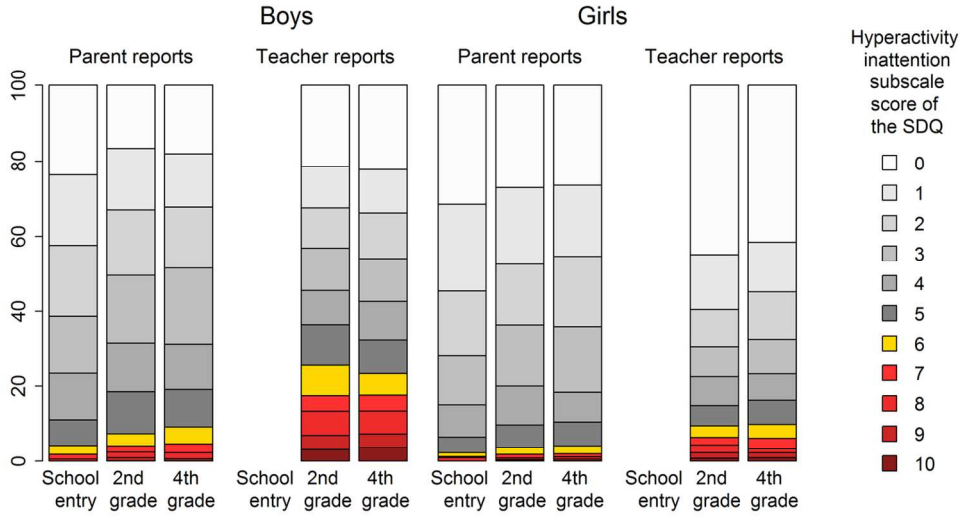

Figure 2 Observed percent distribution of Hyperactivity-Inattention Subscale score stratified by gender, time of observation, and source of information.
The Hyperactivity-Inattention Subscale score ranges from 0 to 10, whereby "indication of ADHD" [borderline (6) and abnormal values (>6)] are indicated by yellow and red colours.

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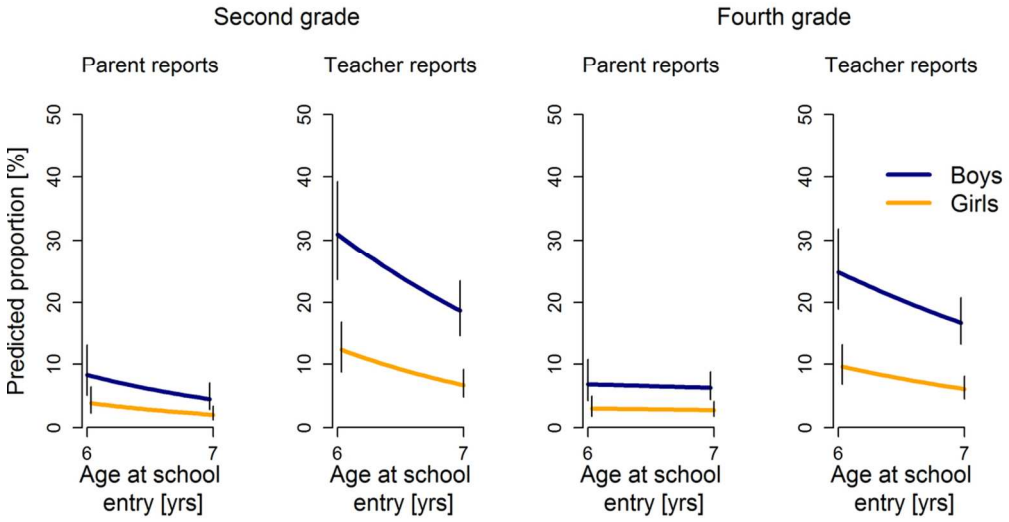

Figure 3 Frequency of predicted ADHD indication stratified by gender, time of observation, and source of information.
Predicted frequencies of ADHD indications are presented for boys and girls, entering school at six or seven years of age, living in a nuclear family, having the highest CASMIN score, and no migrant background. Vertical bars represent 95% confidence intervals.

101x57mm (300 x 300 DPI)

Appendix: Sensitivity analysis

Table 1 Association between age at school entry and Hyperactivity-Inattention Subscale score. Inclusion of children defined by country wide school entry rules. (multivariable linear regression for correlated outcomes; N=2332).

	Second grade						Fourth grade					
	Parent-reports			Teacher-reports			Parent-reports			Teacher-reports		
Set	β	SE	p-value	β	SE	p-value	β	SE	p-value	β	SE	p-value
1)	-0.20	0.17	0.2447	-0.92	0.23	<.0001	-0.17	0.15	0.2773	-0.74	0.21	0.0003
2)	-0.24	0.17	0.1557	-0.95	0.23	<.0001	-0.20	0.15	0.1878	-0.78	0.20	0.0001
3)	-0.31	0.15	0.0422	-0.98	0.24	<.0001	-0.22	0.15	0.1322	-0.77	0.22	0.0006

Set 1: adjusted for gender;
Set 2: adjusted for set 1 plus birth status, family form, CASMIN score, and migrant background;
Set 3: adjusted for set 2 plus parent-reported Hyperactivity-Inattention Subscale score at baseline.
Abbreviations: SE, standard error.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract ✓	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale Page 5&6	2	Explain the scientific background and rationale for the investigation being reported
Objectives Page 6	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design Page 7	4	Present key elements of study design early in the paper
Setting Page 7	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants Page 7&8	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables Page 8&9	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement Page 8 to 10	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias Page 8&9	9	Describe any efforts to address potential sources of bias
Study size Page 7&8	10	Explain how the study size was arrived at
Quantitative variables Page 8 to 10	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods Page 9 to 11	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants Figure 1	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data Page 12 & 13 Table 1	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data Table 2	15*	Report numbers of outcome events or summary measures over time
Main results Page 13 & 14	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses Page 14 & 15	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results Page 16	18	Summarise key results with reference to study objectives
Limitations Page 16	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation Page 16 to 18	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability Page 18	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding Page 20	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.