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Helga Zoëga, Kenneth J. Rothman, Krista F. Huybrechts, Örn Ólafsson, Gísli Baldursson, Anna B. Almarsdóttir, Sólveig Jónsdóttir, Matthías Halldórsson, Sonia Hernández-Diaz and Unnur A. Valdimarsdóttir

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A Population-Based Study of Stimulant Drug Treatment of ADHD and Academic Progress in Children

AUTHORS: Helga Zoëga, PhD,[a,b,c] Kenneth J. Rothman, DrPH,[d,e] Krista F. Huybrechts, PhD,[f] Örn Ólafsson, PhD,[a] Gísli Baldursson, MD,[g] Anna B. Almarsdóttir, PhD,[b] Sólveig Jónsdóttir, PhD,[h,i] Matthías Halldórsson, MD, DPH, DSc,[j] Sonia Hernández-Diaz, MD, DrPH,[k] and Unnur A. Valdimarsdóttir, PhD[a,i]

[a]Center of Public Health Sciences, [b]Faculty of Pharmaceutical Sciences, and [i]Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland; [c]Institute for Translational Epidemiology, Mount Sinai School of Medicine, New York, New York; [d]RTI Health Solutions, Research Triangle Institute, Research Triangle Park, North Carolina; [e]Departments of Epidemiology and Medicine, Boston University Medical Center, Boston, Massachusetts; [f]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; Departments of [g]Child and Adolescent Psychiatry, [h]Neurology, and [j]Psychiatry, Landspitali University Hospital, Reykjavik, Iceland; and [k]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

KEY WORDS
attention-deficit/hyperactivity disorder, pharmacoepidemiology, stimulant treatment, academic performance, children

ABBREVIATIONS
ADHD—attention-deficit/hyperactivity disorder
ATC—Anatomic Therapeutic Chemical
CI—confidence interval
DDD—defined daily dose
N—nervous system
RR—risk ratio

All authors are responsible for the reported research, have seen and approved the final version of the article, and have taken due care to ensure the integrity of the work. Drs Zoëga, Valdimarsdóttir, Hernández-Diaz, and Rothman made substantial contributions to the conception and design of the study; Drs Zoëga, Valdimarsdóttir, and Halldórsson contributed to the acquisition of data; all authors took active part in the analysis and interpretation of data and the drafting and revising of the article; Drs Zoëga and Valdimarsdóttir had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Dr Valdimarsdóttir is the guarantor of this study. The data on which the article is based are readily reproduced on request.

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Address correspondence to Helga Zoëga, PhD, Institute for Translational Epidemiology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1057, New York, NY 10029. E-mail: helga.zoega@mssm.edu

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WHAT'S KNOWN ON THIS SUBJECT: Stimulants are widely used as a therapeutic option in the United States and increasingly in Europe. The effect of stimulant drug treatment on academic performance among children with attention-deficit/hyperactivity disorder is unclear. Long-term follow-up studies on the topic are scarce.

WHAT THIS STUDY ADDS: Our results indicate that earlier stimulant treatment of attention-deficit/hyperactivity disorder is associated with a lower risk of decline in academic performance. Girls show a definite benefit only in mathematics, whereas boys show marginal benefits in both mathematics and language arts.

abstract

OBJECTIVE: We evaluated the hypothesis that later start of stimulant treatment of attention-deficit/hyperactivity disorder adversely affects academic progress in mathematics and language arts among 9- to 12-year-old children.

METHODS: We linked nationwide data from the Icelandic Medicines Registry and the Database of National Scholastic Examinations. The study population comprised 11 872 children born in 1994–1996 who took standardized tests in both fourth and seventh grade. We estimated the probability of academic decline (drop of ≥5.0 percentile points) according to drug exposure and timing of treatment start between examinations. To limit confounding by indication, we concentrated on children who started treatment either early or later, but at some point between fourth-grade and seventh-grade standardized tests.

RESULTS: In contrast with nonmedicated children, children starting stimulant treatment between their fourth- and seventh-grade tests were more likely to decline in test performance. The crude probability of academic decline was 72.9% in mathematics and 42.9% in language arts for children with a treatment start 25 to 36 months after the fourth-grade test. Compared with those starting treatment earlier (≤12 months after tests), the multivariable adjusted risk ratio (RR) for decline was 1.7 (95% confidence interval [CI]: 1.2–2.4) in mathematics and 1.1 (95% CI: 0.7–1.8) in language arts. The adjusted RR of mathematics decline with later treatment was higher among girls (RR, 2.7; 95% CI: 1.2–6.0) than boys (RR, 1.4; 95% CI: 0.9–2.0).

CONCLUSIONS: Later start of stimulant drug treatment of attention-deficit/hyperactivity disorder is associated with academic decline in mathematics. *Pediatrics* 2012;130:e53–e62

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting 5% to 10% of school-aged children in the United States and Europe.[1,2] Drug treatment of ADHD with stimulants (and atomoxetine) is now widely used as a therapeutic option in the United States and increasingly in Europe.[1,3–10] Nevertheless, the increasing use of ADHD drugs is debated, chiefly because of concerns of overuse, addiction, and uncertainty about the long-term outcomes of treatment.

Stimulant treatment consistently has been shown to be effective in improving inattention, hyperactivity, and impulsivity, the core symptoms of ADHD among school-aged children,[11,12] but evidence supporting gains in academic performance is equivocal.[13–15] Controlled trials have reported acutely improved cognitive performance after short durations of treatment,[16–20] but studies on longer-term academic effects in naturalistic settings are scarce. Existing studies, with follow-up periods from 6 to 13 years, have revealed improved performance in mathematics[21,22] but inconsistent results for reading improvement.[21,23] Gender-specific effects have not been reported; several methodologic limitations, including reliance on self-reports of medication use, have hindered interpretation.

In Iceland, the use of methylphenidate stimulants to treat children with ADHD is more common than in most European countries, ~5 times the use in the neighboring Nordic countries, and reportedly similar to use in the United States.[1,24] With ~100% complete national registration of prescription drug utilization and mandatory standardized scholastic tests for all children at age 9 and 12, Iceland offers a unique setting to study academic performance among children who are treated with medication for ADHD.

In this study, we are interested in the effects of stimulant treatment of ADHD on academic progress. Comparing all medicated children with nonmedicated children would be subject to substantial bias from confounding by treatment indication. To limit such bias, we restricted the study to comparisons among children who were treated but whose treatment started at different times. We focused on children starting treatment within the age range of 9 to 12 years and examined the effect of later versus early treatment on academic progress within this group. This restriction leaves a smaller but more homogenous study population, reducing the bias from confounding by indication. Among children treated either early or later within the age range of 9 to 12, we evaluated the hypothesis that a later start of drug treatment for ADHD would adversely affect academic progress in mathematics and language arts.

METHODS

Study Setting and Population

Our source population was all 13 617 children born in 1994, 1995, and 1996 and registered in the Icelandic school system. We obtained data from January 1, 2003 through December 31, 2008 on psychotropic drug prescription fills and standardized test results in mathematics and language arts for this national cohort. By using the personal identification number unique to every citizen, we linked records from the National Population Registry to the Icelandic Medicines Registry and the Database of National Scholastic Examinations. The final study population comprised all children who took a standardized test in both fourth grade (age 9) and seventh grade (age 12) (n = 11 872). Of these children, 11 619 took both mathematics examinations, and 11 542 took both examinations in language arts.

ADHD Drug Exposure

The Icelandic Medicines Registry contains information for each person dispensed prescription drugs as an outpatient since January 1, 2003. Completeness ranges from 93.7% to 99.9% of all dispensed outpatient prescriptions for the years 2003–2008. For each dispensed prescription in the study, we received information on drug name, number of defined daily doses (DDDs), Anatomic Therapeutic Chemical (ATC) code, date, and pharmacy of the filled prescription.

ADHD drugs were defined according to the World Health Organization ATC classification as drugs within the "nervous system" (N) category, pertaining to the category of "centrally acting sympathomimetics" (N06BA).[25] Chemical substances included were amphetamine (N06BA01), methylphenidate (N06BA04), and atomoxetine (N06BA09). Other chem ical substances within the ATC category N06BA were not available in Iceland or not prescribed to children at the time during the study period. All drugs included had ADHD as their main indication, according to clinical guidelines and drug package inserts.[26,27] The Icelandic Medicines Registry does not hold information on the indication for drug treatment. In Iceland, however, an ADHD diagnosis must be verified by a pediatric, psychiatric, or neurologic specialist for reimbursement, so it is reasonable to assume that essentially all medicated children fulfilled the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria[28] for ADHD before treatment.

We defined the start of therapy to be the first prescription after a period of at least 11 months during which no prescriptions for an ADHD drug were filled. After this period, we considered the start date of treatment for each child to be the date of the first dispensing of a prescription for an ADHD drug (stimulant or atomoxetine). To reduce confounding by indication, we restricted the main analysis to children who started treatment between test dates in fourth and seventh grade. We categorized medicated children according to the timing

of their treatment initiation after their fourth-grade test: within 12 months, 13 to 24 months, or 25 to 36 months after the fourth-grade test. The last category we designated as later treatment. The total number of filled DDDs corresponds to the cumulative drug exposure for each child. The DDD is defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology. Complete compliance with this technical unit of measurement (the equivalent of 30 mg of methylphenidate, 80 mg of atomoxetine, or 15 mg of amphetamine per day) would result in the cumulative DDD for each child being equal to the number of treatment days from start to test day. But because children might take more or <1 DDD each day, the cumulative DDD may not necessarily be equal to the number of treatment days. We considered treatment to have been discontinued early if children filled <90 DDDs of an ADHD drug. We classified children as treated on their test day in seventh grade if the number of DDDs on the last prescription overlapped with the test day.

We assumed that children were being treated concurrently with other psychotropic drugs if a prescription was filled for another psychotropic drug within the 90-day period after the dispensing of an ADHD drug. Other psychotropic drugs were defined as all drugs, other than ADHD drugs, pertaining to ATC drug category N, including antidepressants (N06A), antipsychotics (N05A), anxiolytics, hypnotics and sedatives (N05B, N05C), and other psychotropic drugs (N01, N02, N03, N04, N06C, N06D, N07).

Academic Outcomes

The standardized tests in mathematics and language arts are nationally coordinated assessments within the Icelandic school system, mandatory for all children in fourth grade (9-year-olds) and seventh grade (12-year-olds). We obtained the test scores, test dates, school name, and school region for each child who took tests during 2003–2008. Some test scores were missing owing to disability, illness on the test day, migration to or from Iceland between tests, or unspecified absence.

Tests are scored on a scale of 0.0 to 10.0. We converted the scores to percentiles. We measured change in performance by subtracting the fourth-grade percentile rank from the seventh-grade rank. We defined an academic decline to be a drop of ≥5.0 percentile points.

Data Analysis

We described medicated and nonmedicated populations by demographic characteristics and by ADHD drug treatment (ie, type of drugs used, early discontinuation, concurrent psychotropic drug treatment, and treatment on test day) according to time of treatment start. We estimated risks, as well as risk ratios (RRs) and differences, for a drop in performance in the mathematics and language arts test. First we estimated crude measures, and then we controlled for performance level on the fourth-grade test (categorized into terciles), gender, birth month (categorized as January–May, June–August, September–December), birth place (urban, rural, outside Iceland), school region (urban, rural), change of schools, concurrent psychotropic drug treatment, treatment on test day, and early discontinuation of ADHD drug treatment (<90 DDDs). For stratified analyses, we standardized results to the distribution of the total medicated test-participating population 2003–2008.[29] In these analyses, we excluded children who scored in the lowest fifth percentile on the fourth-grade test, because they were unable to decline in rank by at least 5.0 percentile points. We also conducted a modified Poisson regression analysis to adjust for all confounders simultaneously.[30] Finally, we ran a sensitivity analysis to assess the influence of selection bias that would result if untested children had a different association between later treatment start and academic decline than the children tested.[31] We assumed a range of reference risks and RRs in the group of children not taking either or both examinations. For those who received early treatment, we assumed values of 25%, 33%, 50%, and 75% for the risk of academic decline. To each of these assumed values, we then applied a range of 0% to 100% risk of decline for children who received later treatment, because they could have had either a greater or lesser academic decline than test-participating children. These assumptions produced a range of RRs from 0.0 to 4.0 among non–test participants with later treatment, which we then took into account to get an overall estimate that included projected results from these missing children.

We used PASW Statistics (version 18; SPSS Inc, Chicago, IL) and Excel spreadsheets (Microsoft, Redmond, WA) to run analyses. This study was approved by the National Bioethics Committee (VSNb2008040016/03-7) and the Data Protection Authority (2008040343) in Iceland.

RESULTS

Of the 13 617 children registered in the Icelandic school system, 1029 children (8%) were treated with ADHD drugs at any time during the study period. Test participation, that is, children taking tests in both fourth and seventh grade in either mathematics or language arts, was lower for the total medicated population (72%) than the nonmedicated general population (88%) (Fig 1). Of 317 children who began treatment between the fourth- and seventh-grade tests, 236 took both tests, resulting in 65%, 85%, and 75% participation for children starting medication at ≤12 months, 13 to 24 months, and 25 to 36 months, respectively, after the date of fourth-grade

tests. Demographic and baseline characteristics among test participants varied only slightly by timing of treatment start (Table 1). Overall, boys were more likely to be medicated than girls, as were children born in the last third of the calendar year compared with those born earlier. Medicated children scored considerably lower on their fourth-grade tests (taken before their start of treatment) than the nonmedicated population.

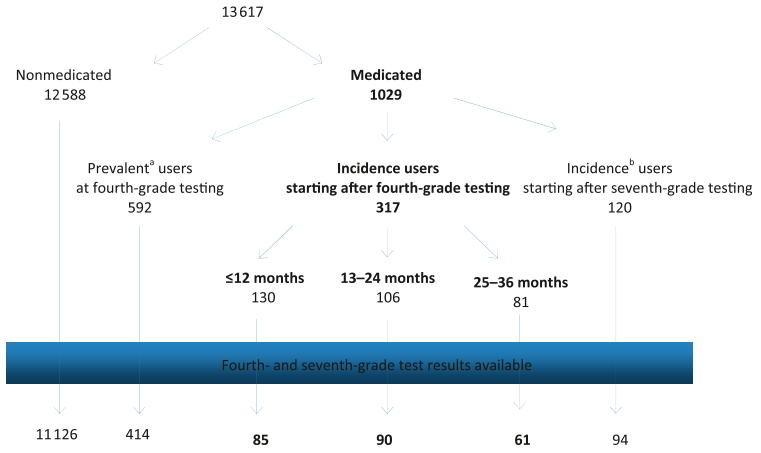

FIGURE 1
Origin of study population. [a] Prevalent users are children already being treated before the fourth-grade tests. [b] Incidence users are children who began treatment after the fourth-grade tests.

TABLE 1 Characteristics of Study Population by Exposure to ADHD Drug Treatment

	Nonmedicated Population, *n* (%)	Medicated Population, Time Since Fourth-Grade Test Until ADHD Drug Treatment, *n* (%)		
		≤12 mo	13–24 mo	25–36 mo
Total	11 126 (100)	85 (100)	90 (100)	61 (100)
Gender				
Male	5458 (49)	59 (69)	65 (72)	41 (67)
Female	5668 (51)	26 (31)	25 (28)	20 (33)
Birth year				
1994	3751 (34)	36 (42)	34 (38)	17 (28)
1995	3636 (33)	17 (20)	28 (31)	22 (36)
1996	3739 (34)	32 (38)	28 (31)	22 (36)
Birth month				
January–April	3682 (33)	23 (27)	26 (29)	18 (30)
May–August	3895(35)	24 (28)	27 (30)	19 (31)
September–December	3459 (32)	38 (45)	37 (41)	24 (39)
Birth place				
Urban	6906 (62)	56 (66)	64 (71)	38 (62)
Rural	3522 (32)	24 (28)	22 (24)	19 (31)
Outside Iceland	698 (6)	5 (6)	4 (4)	4 (7)
School region, fourth grade				
Urban	6627 (60)	52 (61)	64 (71)	42 (69)
Rural	4499 (40)	33 (39)	26 (29)	19 (31)
Mathematics test, fourth-grade percentile rank				
66.7th–100th	3803 (34)	10 (12)	13 (15)	8 (14)
33.4th–66.6th	3699 (34)	21 (25)	21 (24)	14 (24)
0.1–33.3rd	3512 (32)	52 (63)	55 (62)	36 (62)
Language arts test, fourth-grade percentile rank				
66.7th–100th	3815 (35)	5 (6)	8 (9)	5 (8)
33.4th–66.6th	3706 (34)	23 (27)	17 (19)	20 (33)
0–33.3rd	3459 (31)	57 (67)	63 (72)	35 (58)

Total number of children registered in the Icelandic school system was 13 617, of whom 11 872 (87.2%) took standardized tests in fourth and seventh grade: 746 of 1029 (72.5%) in the medicated population and 11 126 of 12 588 (88.4%) in the nonmedicated population.

Nearly all medicated test-participating children were treated with methylphenidate (96%); 9% were treated simultaneously with the nonstimulant atomoxetine, and 34% were treated concurrently with another psychotropic drug (Table 2). Methylphenidate was used mainly in extended-release formulations. Of the medicated population, 14% discontinued treatment within 3 months of initiation; that is, they filled <90 DDDs of an ADHD drug. Children who started treatment within 12 months after fourth-grade tests received, on average, more than double the supply (filled DDDs) of ADHD drugs before tests in seventh grade, compared with those who started later (Table 2).

Change in Academic Performance

Among children in the nonmedicated general population, performance on average did not change much between tests in fourth and seventh grade; the crude mean percentile score change was a rise of 0.4 (95% confidence interval [CI]: 0.0–0.8) in mathematics and 0.0 (95% CI: −0.3 to 0.4) in language arts. In contrast, mean performance level among medicated children declined. The decline was concentrated among those with later treatment initiation and was much more striking for mathematics than for language arts, with a mean decline of 9.4 percentile points in mathematics for those with delayed treatment initiation (Table 3). In mathematics, the risk of a decline of ≥5.0 percentile points was high among all medicated students, but especially high (crude RR: 1.8; 95% CI: 1.3–2.5) for children who started treatment 25 to 36 months after their fourth-grade test. The absolute increase in risk of a decline in mathematics for the later starters on medication was 32%

TABLE 2 Characteristics of ADHD Drug Treatment Among Medicated Children

	Time Since Fourth-Grade Test Until ADHD Drug Treatment		
	≤12 mo	13–24 mo	25–36 mo
Children treated with			
Any ADHD drug, *n* (%)	85 (100)	90 (100)	61 (100)
Methylphenidate, *n* (%)	84 (99)	87 (97)	55 (90)
Atomoxetine, *n* (%)	10 (12)	11 (12)	11 (18)
Both, *n* (%)	9 (11)	8 (9)	5 (8)
Mean age, y (minimum–maximum) at treatment start	9.8 (9.0–10.7)	10.7 (10.0–11.6)	11.7 (11.0–12.7)
Mean No. (minimum–maximum) of DDDs[a]			
Between fourth- and seventh-grade test	427 (10–1972)	325 (10–1188)	175 (6–594)
Over total study period	662 (10–4302)	547 (10–2250)	361 (20–1278)
Discontinued treatment early (<90 DDDs)			
No, *n* (%)	67 (79)	77 (86)	53 (87)
Yes, *n* (%)	18 (21)	13 (14)	8 (13)
Treated on test day, seventh grade			
Yes, *n* (%)	34 (40)	35 (39)	41 (67)
No, *n* (%)	51 (60)	55 (61)	20 (33)
Treated concurrently[b] with			
Any psychotropic drug, *n* (%)	33 (39)	22 (24)	25 (41)
Antidepressants, *n* (%)	25 (29)	20 (22)	17 (28)
Amitryptiline, *n* (%)	12 (14)	8 (9)	5 (8)
Antipsychotic, *n* (%)	12 (14)	7 (8)	12 (20)
Anxiolytic or hypnotic and sedative, *n* (%)	0 (0)	1 (1)	2 (3)
Other psychotropic drugs, *n* (%)	4 (5)	5 (6)	3 (4)

[a] One DDD equals 30 mg of methylphenidate, 80 mg of atomoxetine, or 15 mg of amphetamine.

[b] Concurrent treatment defined as a filled prescription for another psychotropic drug within 3 months after a prescription filled for an ADHD drug (ATC group N06BA).

TABLE 3 Crude Risks, Risk Differences, and RRs of Academic Decline (≥5 Percentile Points) According to Timing of ADHD Drug Treatment Initiation

Mathematics	ADHD Drug Treatment Started, No. of Months After Fourth- Grade Test		
	≤12 mo	13–24 mo	25–36 mo
Mean percentile score change (95% CI)	−0.3 (−4.8 to 4.3)	−5.7 (−10.5 to 1.0)	−9.4 (−14.4 to −1.4)
Declined in performance ≥5.0 percentile points, *n*	28	36	35
Total, *n*	68	76	48
Crude risk, %	41	47	73
Risk difference, % (95% CI)	0.0 (ref)	6 (−10 to 22)	32 (14 to 48)
RR (95% CI)	1.0 (ref)	1.2 (0.80 to 1.7)	1.8 (1.3 to 2.5)
Language arts			
Mean percentile score change (95% CI)	0.7 (−3.4 to 4.8)	−1.7 (−5.4 to 2.0)	−3.4 (−9.2 to 2.5)
Declined in performance ≥5.0 percentile points, *n*	25	31	21
Total, *n*	65	72	49
Crude risk, %	39	43	43
Risk difference, % (95% CI)	0.0 (ref)	5 (−12 to 21)	4 (−14 to 22)
RR (95% CI)	1.0 (ref)	1.1 (0.75 to 1.7)	1.1 (0.71 to 1.7)

ref, reference.

(95% CI: 14%–48%). For language arts, in contrast, the crude RR of academic decline with later treatment was 1.1 (95% CI: 0.7–1.7), and the absolute increase in risk for academic decline among later starters was only 4% (95% CI: −14% to 22%).

Table 4 shows the results for mathematics stratified singly by children's performance level on their fourth-grade test, gender, and concurrent psychotropic drug treatment. In each stratified display, there is some variation in the estimates across strata, but in each case the standardized estimates were similar to the crude estimates, indicating little confounding by each of the stratification variables. Later treatment had a larger effect for children who scored in the lowest third (RR: 2.1) and middle third (RR: 1.9) on their fourth-grade test than for those who scored in the highest third (RR: 1.1). The absolute risk of academic decline in mathematics was higher for girls than boys (86.7% vs 66.7%), as was the RR: 3.6 for girls versus 1.4 for boys. Furthermore, the effect of later treatment start was slightly stronger for children not receiving any concurrent psychotropic drug treatment than for those treated concurrently with other psychotropic drugs. The estimated effect was increased for children still being treated with ADHD drugs on their test day in seventh grade (RR: 1.9) compared with those no longer being treated on test day (RR: 1.5).

Table 5 shows the association between later start of ADHD drug treatment and decline in language arts performance stratified by children's performance on their fourth-grade test, gender, and concurrent psychotropic drug treatment. The adjusted effect estimates did not differ much from the crude estimates and indicated weak associations. The estimated effect of later treatment on decline in language arts was elevated slightly for boys (RR: 1.5), but showed an inverse association for girls (RR: 0.6). There was an effect among those still being treated on test day in seventh grade (RR: 1.6), but not among those no longer being treated (RR: 0.8).

The adjusted estimates of the effect of later drug treatment on academic performance remained the same or changed only minimally when we

TABLE 4 Stratified Risks and Standardized Effect Estimates of Decline in Mathematics According to Timing of ADHD Drug Treatment Initiation

	Time Since Fourth-Grade Test Until ADHD Drug Treatment		
	≤12 mo	13–24 mo	25–36 mo
Performance on fourth-grade test			
Scored in lowest third			
Declined in performance ≥5.0 percentile points, *n*	11	14	16
Total, *n*	38	42	26
Risk, %	29	33	62
Scored in middle third			
Declined in performance ≥5.0 percentile points, *n*	9	12	12
Total, *n*	20	21	14
Risk, %	45	57	86
Scored in highest third			
Declined in performance ≥5.0 percentile points, *n*	8	10	7
Total, *n*	10	13	8
Risk, %	80	77	88
Standardized risk, %	42	47	73
Standardized risk difference, % (95% CI)	0 (ref)	5 (−10 to 21)	31 (14 to 47)
Standardized RR (95% CI)	1.0 (ref)	1.1 (0.79 to 1.6)	1.7 (1.3 to 2.4)
Gender			
Boys			
Declined in performance ≥5.0 percentile points, *n*	23	26	22
Total, *n*	47	55	33
Risk, %	49	47	67
Girls			
Declined in performance ≥5.0 percentile points, *n*	5	10	13
Total, *n*	21	21	15
Risk, %	24	48	87
Standardized risk, %	42	47	72
Standardized risk difference, % (95% CI)	0 (ref)	6 (−11 to 22)	31 (13 to 48)
Standardized RR (95% CI)	1.0 (ref)	1.1 (0.79 to 1.6)	1.7 (1.3 to 2.4)
Concurrent psychotropic drug treatment			
No			
Declined in performance ≥5.0 percentile points, *n*	14	26	18
Total, *n*	42	57	27
Risk, %	33	46	67
Yes			
Declined in performance ≥5.0 percentile points, *n*	14	10	17
Total, *n*	26	19	21
Risk, %	54	53	81
Standardized risk, %	43	49	73
Standardized risk difference, % (95% CI)	0 (ref)	6 (−12 to 24)	30 (13 to 48)
Standardized RR (95% CI)	1.0 (ref)	1.1 (0.77 to 1.7)	1.7 (1.2 to 2.4)

Standardized to the distribution of the total medicated test-participating population, 2003–2008. ref, reference.

stratified the data by other covariates (ie, birth year, birth month, birth place, school region, and change of school; data not shown), indicating only negligible confounding by these variables.

Similarly, the RRs reported in Tables 3 to 5 remained nearly the same when controlling simultaneously for all covariates in a Poisson regression analysis: RR = 1.7 (95% CI: 1.2–2.4) in mathematics and RR = 1.1 (95% CI: 0.7–1.8) in language arts. Compared with the nonmedicated general population, we found that the adjusted risk of academic decline was 1.6 times greater (95% CI: 1.4–1.8) in mathematics and 1.3 times greater (95% CI: 1.1–1.6) in language arts for children who started treatment any time between tests in fourth and seventh grade.

Sensitivity Analysis

Figure 2 displays the estimated RR from the main analysis adjusted for hypothetical selection bias (y axis) given the assumed RRs among non–test participants (x axis). The depicted lines, 1 for each assumed reference risk, represent adjusted RRs for a range of associations between later treatment and academic decline among non–test participant children. These adjusted RRs varied from 1.0 to 2.2 in mathematics and from 0.6 to 1.7 in language arts. The sensitivity analysis indicates that the basic findings would look roughly the same over a broad range of assumptions about the risks and associations among children who did not take both tests.

DISCUSSION

The results of this population-based, nationwide study indicate that earlier treatment with ADHD drugs between the ages of 9 and 12 years is associated with a lower risk of a decline in academic performance, particularly in mathematics. Our data reveal that the apparent advantage of earlier treatment differs for boys and girls. Girls show a definite benefit only in mathematics, whereas boys show marginal benefits in both mathematics and language arts.

The study has several important limitations. First, we have no information about the underlying ADHD diagnosis, subtype, severity of the condition, or potential comorbid learning or psychiatric disorders. In Iceland, the studied

TABLE 5 Stratified Risks and Standardized Effect Estimates of Decline in Language Arts According to Timing of ADHD Drug Treatment Initiation

	Time Since Fourth-Grade Test Until ADHD Drug Treatment		
	≤12 mo	13–24 mo	25–36 mo
Performance on fourth-grade test			
Scored in lowest third			
Declined in performance ≥5.0 percentile points, *n*	11	16	7
Total, *n*	38	47	24
Risk, %	29	34	29
Scored in middle third			
Declined in performance ≥5.0 percentile points, *n*	11	10	10
Total, *n*	22	17	20
Risk, %	50	59	50
Scored in highest third			
Declined in performance ≥5.0 percentile points, *n*	3	5	4
Total, *n*	5	8	5
Risk, %	60	63	80
Standardized risk, %	38	44	41
Standardized risk difference, % (95% CI)	0 (ref)	6 (−11 to 22)	3 (−16 to 21)
Standardized RR (95% CI)	1.0 (ref)	1.2 (0.77 to 1.7)	1.1 (0.67 to 1.7)
Gender			
Boys			
Declined in performance ≥5.0 percentile points, *n*	14	24	16
Total, *n*	42	51	31
Risk, %	33	47	52
Girls			
Declined in performance ≥5.0 percentile points, *n*	11	7	5
Total, *n*	23	21	18
Risk, %	48	33	28
Standardized risk, %	38	43	45
Standardized risk difference, % (95% CI)	0 (ref)	6 (−11 to 22)	7 (−11 to 26)
Standardized RR (95% CI)	1.0 (ref)	1.2 (0.76 to 1.7)	1.2 (0.76 to 1.9)
Concurrent psychotropic drug treatment			
No			
Declined in performance ≥5.0 percentile points, *n*	13	23	8
Total, *n*	38	53	28
Risk, %	34	43	29
Yes			
Declined in performance ≥5.0 percentile points, *n*	12	8	13
Total, *n*	27	19	21
Risk, %	44	42	62
Standardized risk, %	39	43	44
Standardized risk difference, % (95% CI)	0 (ref)	4 (−14 to 21)	5 (−13 to 23)
Standardized RR (95% CI)	1.0 (ref)	1.1 (0.71 to 1.7)	1.1 (0.73 to 1.8)

Standardized to the distribution of the total medicated test-participating population, 2003–2008. ref, reference.

drugs are not reimbursable unless a diagnosis for ADHD has been made by a specialist. To limit confounding by indication, we restricted the primary comparison with children who started treatment for ADHD sometime between their tests in fourth and seventh grade, so that all in the analysis had indications for ADHD treatment at some point. Confounding by indication still may arise from differences that relate to the age at initiation of treatment. Children with severe symptoms and more persistent academic problems might be expected to begin treatment with medication earlier than those with less severe symptoms. Our results, however, indicate that those who started drug treatment soonest after the fourth-grade test declined the least academically in mathematics. The cumulative drug exposure for these children was, on average, double the exposure of those with later treatment. Further, analyses that included children who started treatment before the fourth-grade test and after the seventh-grade test resulted in the same basic pattern of results (data not shown). We attempted to capture coexisting psychiatric disorders by accounting for concurrent psychotropic drug treatment and found that the observed effect of late treatment on academic performance was stronger among those medicated exclusively with stimulants, that is, not concurrently with other psychotropic drugs. Comorbid learning disabilities could confound our results if diagnosed between tests and related to timing of medication start. The reported associations could either be exaggerated, if such a diagnosis would lead to a delay in drug treatment start, or underestimated, if the diagnosis accelerated treatment start.

Second, the study lacks information on concurrent behavioral therapy or educational school services received by children in the study population. Availability of such services in Iceland is low, however, and in light of evidence indicating that combined therapy provides only modest advantages compared with drug treatment alone,[12,32] this limitation may not be of major concern. Third, it is possible that children initiating treatment earlier also have more family or social support that aids their academic performance. Because our findings are based not on a single test result but on self-matched comparisons that contrast seventh-grade test results with fourth-grade test results, family setting would not confound the results

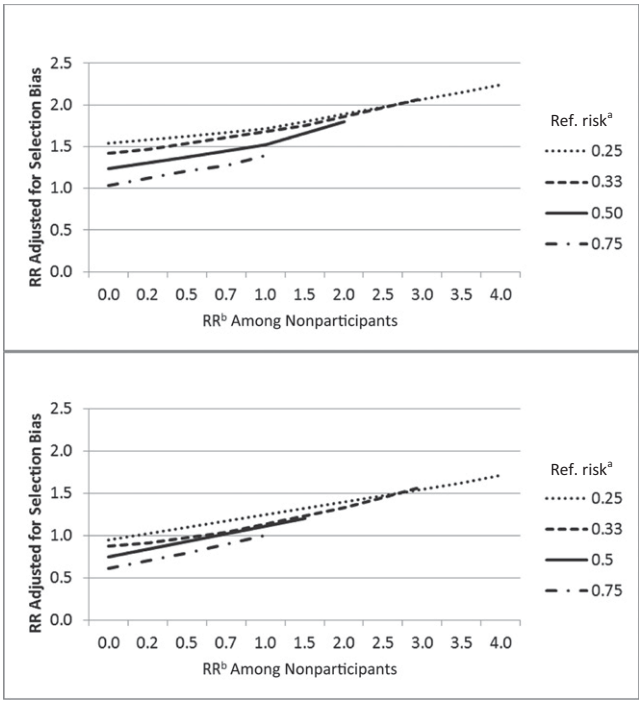

FIGURE 2

Analysis correcting for possible selection bias, assuming a range of risks of academic decline for non–test participants. (Mathematics decline is shown in upper panel; language arts decline is shown in lower panel.) [a] Ref. risk, risk of academic decline in non–test participants who started treatment early (≤12 months after fourth-grade tests). [b] RR, academic decline in children who started treatment later (25–36 months after fourth-grade tests) versus those who started early (≤12 months after fourth-grade tests).

unless it had different age-specific effects on test performance or the family dynamic had changed during the time between the 2 tests. Such effects are possible. For example, parents could become increasingly aware of the child's problem after the fourth-grade test results and take additional measures to improve academic performance.Fourth, the study would have been stronger if it included children with ADHD who were prescribed stimulants but did not actually take any medication, to account for the effects of only seeking treatment.

Our study population is limited to examination takers in both fourth and seventh grade, and test participation, as expected, was lower among the medicated population than the nonmedicated population. Test participation also varied between early and late treatment initiators between the fourth- and seventh-grade tests. We assessed this potential source of bias with a sensitivity analysis. Assuming a null association among the non–test participants, we found that the adjusted main effect estimates did not vary greatly from those reported among test participants. We caution that our main findings, however, may not apply to children too impaired by ADHD or its comorbidities to participate in regular school activities.

Consistent with the previously established association between ADHD and poor academic outcomes,[22,33–35] we found that children medicated for ADHD fare worse academically compared with their nonmedicated peers and that their performance generally declines with time, particularly in mathematics, when initiation of drug treatment is delayed.

Previous studies lend support to some of our findings. Interestingly, Molina et al[22] found that mathematics scores were the only functional outcome positively associated with past-year parent-reported medication use during follow-up of participants of the Multimodal Treatment Study of Children with ADHD at years 3, 6, and 8 after enrollment, suggesting a beneficial effect of continued medication treatment that may be unique to mathematic achievement. Studies indicate that language disorders and mathematical disability have separate cognitive profiles.[36] Possibly, stimulant drug treatment has more positive effects on the cognitive function underlying mathematical ability than on that underlying language ability. Scheffler et al[21] recently found that parent-reported drug treatment was associated with higher mathematic achievement test scores within a US sample of 594 elementary school children with ADHD, but higher reading scores were dependent on longer treatment durations. Barbaresi et al[23] demonstrated that stimulant treatment of children with ADHD was associated with improved reading achievement, decreased school absenteeism, and decreased grade retention within a population-based sample of 349 children diagnosed with ADHD.

The gender difference in our data could reflect random variability from small numbers, but it also might be consequent to real differences in the academic benefit of stimulant treatment. Girls diagnosed with ADHD present predominantly with symptoms of inattention and have lower levels of hyperactivity than boys with ADHD,[37,38] which may play a role in how early the disorder is detected and when treatment starts. Previous studies, however, have found neither gender nor ADHD subtype as modifiers of stimulant treatment outcomes.[20,39,40] The results of this nationwide follow-up study indicate that early, rather than later, initiation of drug treatment is associated with a reduced risk of declining academic performance among boys and girls with ADHD, especially in mathematics.

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REFERENCES

1. Centers for Disease Control and Prevention. Mental health in the United States: prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder—United States, 2003. *MMWR Mortal Wkly Rep*. 2005;54(34):842–847
2. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*. 2007;164(6):942–948
3. Zoëga H, Baldursson G, Halldórsson M. Use of methylphenidate among children in Iceland 1989-2006 [in Icelandic]. *Laeknabladid*. 2007;93(12):825–832
4. Zoëga H, Baldursson G, Hrafnkelsson B, Almarsdóttir AB, Valdimarsdóttir U, Halldórsson M. Psychotropic drug use among Icelandic children: a nationwide population-based study. *J Child Adolesc Psychopharmacol*. 2009; 19(6):757–764
5. Castle L, Aubert RE, Verbrugge RR, Khalid M, Epstein RS. Trends in medication treatment for ADHD. *J Atten Disord*. 2007;10(4):335–342
6. Zuvekas SH, Vitiello B, Norquist GS. Recent trends in stimulant medication use among U.S. children. *Am J Psychiatry*. 2006;163(4): 579–585
7. Hsia Y, Maclennan K. Rise in psychotropic drug prescribing in children and adolescents during 1992-2001: a population-based study in the UK. *Eur J Epidemiol*. 2009;24(4):211–216
8. Faber A, de Jong-van den Berg LT, van den Berg PB, Tobi H. Psychotropic co-medication among stimulant-treated children in The Netherlands. *J Child Adolesc Psychopharmacol*. 2005;15(1):38–43
9. Knellwolf AL, Deligne J, Chiarotti F, et al. Prevalence and patterns of methylphenidate use in French children and adolescents. *Eur J Clin Pharmacol*. 2008;64(3):311–317
10. Scheffler RM, Hinshaw SP, Modrek S, Levine P. The global market for ADHD medications. *Health Aff (Millwood)*. 2007;26(2):450–457
11. Greenhill LL, Halperin JM, Abikoff H. Stimulant medications. *J Am Acad Child Adolesc Psychiatry*. 1999;38(5):503–512
12. The MTA Cooperative Group; Multimodal Treatment Study of Children with ADHD. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56(12): 1073–1086
13. Conner D. Stimulants. In: Barkley R, ed. Attention-Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment. 3rd ed. New York, NY: The Guilford Press; 2005:608–647
14. Brown RT, Amler RW, Freeman WS, et al; American Academy of Pediatrics Committee on Quality Improvement; American Academy of Pediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. *Pediatrics*. 2005;115(6). Available at: www.pediatrics.org/cgi/content/full/115/6/e749
15. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics*. 2004;113(4):762–769
16. Swanson J, Baler RD, Volkow ND. Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology*. 2011; 36(1):207–226
17. Pietrzak RH, Mollica CM, Maruff P, Snyder PJ. Cognitive effects of immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Neurosci Biobehav Rev*. 2006;30(8):1225–1245
18. Bedard AC, Jain U, Johnson SH, Tannock R. Effects of methylphenidate on working memory components: influence of measurement. *J Child Psychol Psychiatry*. 2007;48(9):872–880
19. James RS, Sharp WS, Bastain TM, et al. Double-blind, placebo-controlled study of single-dose amphetamine formulations in ADHD. *J Am Acad Child Adolesc Psychiatry*. 2001;40(11):1268–1276
20. Gorman EB, Klorman R, Thatcher JE, Borgstedt AD. Effects of methylphenidate on subtypes of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2006; 45(7):808–816
21. Scheffler RM, Brown TT, Fulton BD, Hinshaw SP, Levine P, Stone S. Positive association between attention-deficit/ hyperactivity disorder medication use and academic achievement during elementary school. *Pediatrics*. 2009; 123(5):1273–1279
22. Molina BS, Hinshaw SP, Swanson JM, et al; MTA Cooperative Group. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(5):484–500
23. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Modifiers of long-term school outcomes for children with attention-deficit/hyperactivity disorder: does treatment with stimulant medication make a difference? Results from a population-based study. *J Dev Behav Pediatr*. 2007;28 (4):274–287
24. Zoëga H, Furu K, Halldórsson M, Thomsen PH, Sourander A, Martikainen JE. Use of ADHD drugs in the Nordic countries: a population-based comparison study. *Acta Psychiatr Scand*. 2011;123(5):360–367
25. WHO. WHO Collaborating Centre for Drug Statistics Methodology: ATC/DDD Index. Oslo, Norway: World Health Organization; 2008
26. Baldursson G, Magnusson P, Haraldsson HM, Halldorsson M. *Vinnulag við greiningu og meðferð athyglisbrests með ofvirkni (ADHD)* [*Clinical Guidelines for Diagnosing and Treating ADHD*]. Seltjarnarnes, Iceland: *Directorate of Health in Iceland*; 2007
27. Icelandic Medicines Agency. *Summaries of Product Characteristics (SPC)*. Seltjarnarnes, Iceland: *Iceland Medicines Control Agency*; 2003–2008
28. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000
29. Greenland S. Applications of Stratified Analysis Methods. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008
30. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7): 702–706

31. Fox T, Fink A, Lash T. Selection bias. In: Fox T, Fink A, Lash T, eds. *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York, NY: Springer; 2009:43–59
32. Hechtman L, Abikoff H, Klein RG, et al. Academic achievement and emotional status of children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):812–819
33. Polderman TJ, Boomsma DI, Bartels M, Verhulst FC, Huizink AC. A systematic review of prospective studies on attention problems and academic achievement. *Acta Psychiatr Scand*. 2010;122(4):271–284
34. Loe IM, Feldman HM. Academic and educational outcomes of children with ADHD. *J Pediatr Psychol*. 2007;32(6):643–654
35. Faraone SV, Biederman J, Lehman BK, et al. Intellectual performance and school failure in children with attention deficit hyperactivity disorder and in their siblings. *J Abnorm Psychol*. 1993;102(4):616–623
36. Landerl K, Fussenegger B, Moll K, Willburger E. Dyslexia and dyscalculia: two learning disorders with different cognitive profiles. *J Exp Child Psychol*. 2009;103(3):309–324
37. Gaub M, Carlson CL. Gender differences in ADHD: a meta-analysis and critical review. *J Am Acad Child Adolesc Psychiatry*. 1997;36(8):1036–1045
38. Gershon J. A meta-analytic review of gender differences in ADHD. *J Atten Disord*. 2002;5(3):143–154
39. MTA Cooperative Group. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: the Multimodal Treatment Study of children with Attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56(12):1088–1096
40. Günther T, Herpertz-Dahlmann B, Konrad K. Sex differences in attentional performance and their modulation by methylphenidate in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2010;20(3):179–186

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A Population-Based Study of Stimulant Drug Treatment of ADHD and Academic Progress in Children

Helga Zoëga, Kenneth J. Rothman, Krista F. Huybrechts, Örn Ólafsson, Gísli Baldursson, Anna B. Almarsdóttir, Sólveig Jónsdóttir, Matthías Halldórsson, Sonia Hernández-Diaz and Unnur A. Valdimarsdóttir

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