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Association between medication use and the performance of higher education entrance tests in individuals with attention deficit-hyperactivity disorder

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Key Points

Question: Can ADHD medications improve performance of higher education entrance test for individuals with ADHD?

Findings: In within-patient analysis, including 930 individuals with ADHD, the test scores were significantly higher during medicated periods as compared to non-medicated periods.

Meaning: Treating patients with ADHD medication might help to improve their academic performance.

Abstract

IMPORTANCE

Individuals with attention-deficit/hyperactivity disorder (ADHD) are at greater risk for academic problems. Pharmacologic treatment is effective in reducing core symptoms of ADHD, but it is unclear whether it helps to improve academic outcomes.

OBJECTIVE

To investigate the association of the use of ADHD medication and the performance of higher education entrance test in individuals with ADHD.

DESIGN, SETTING, AND PARTICIPANTS

This cohort study followed 61,640 individuals with a diagnosis of ADHD from January 01, 2006 to December 31, 2013. Using Swedish national registers, we extracted records of their pharmacological treatment along with data from the Sweden Scholastic Aptitude Test. Using a within-patient design, we compared test scores when patients were taking medication for ADHD with scores when they were not.

EXPOSURES

Periods with and without ADHD medications.

MAIN OUTCOMES AND MEASURES

Scores from the higher education entrance examination.

RESULTS

Within 930 individuals who had taken multiple tests (2524 tests) and used ADHD medications intermittently (mean [SD] age, 22.2 [3.2] years; 493 [53%] males), the test scores were on average 4.8 points higher (95% confidence interval, 2.26 to 7.34; on the scale of 0-200) during medicated periods as compared to non-medicated periods, after adjusting for age and practice

effects. Similar associations between ADHD medications and the test scores were detected in sensitivity analyses.

CONCLUSIONS AND RELEVANCE

Individuals with ADHD scored higher at the higher education entrance tests during medicated versus non-medicated periods. This study suggests that ADHD medications may help ameliorate educationally relevant outcomes in individuals with ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder among children and adolescents which can persist to adulthood.[1] It affects approximately 5-7% of the school-aged population,[2-4] and slightly under 3% in adults.[5-7] On average, individuals with ADHD earn lower school grades or standardized test scores, and they receive less schooling, compared with peers.[8-10] The core symptoms of ADHD, including inattention, impulsivity and hyperactivity, may affect school performance; associated deficits, such as in attention span and working memory, may exacerbate academic difficulties.[11,12]

Clinical trials have shown that ADHD medications are efficacious in reducing the core symptoms of ADHD[13] and are generally tolerated in children, adolescents and adults,[5,14] even though recent Cochrane systematic reviews graded these evidence as low quality.[15,16] It is, however, less clear whether such improvement in behavior translates into better academic outcomes. Results from previous studies are mixed, and more importantly, it is difficult to evaluate the educational significance of the measured outcomes.[17-20]

Using information from the Swedish National Registers, we examined the link between the use of ADHD medication and a nationally valued academic outcome in people who have received a diagnosis of ADHD. We chose a within-patient design, in which the same individual's test scores were examined when they were on and off medication.

Methods

Patients

We used the National Patient Register[21] to identify a total of 61,640 individuals with ADHD (code 314 in ICD-9 and F90 in ICD-10) born between 1976 and 1996. We followed these individuals from January 01, 2006 to December 31, 2013. The Migration and Cause of Death Registers were linked, using the unique personal identification number, to refine individual follow-up periods. The Integrated Database for Labor Market Research and the Swedish Military Service Conscription Register were linked to obtain information on parents' highest educational level and the individual's intelligence quotient (IQ) respectively.

The study was approved by the regional ethics review board in Stockholm, Sweden. By Swedish law, there is no requirement for informed consent in register based research.

Measures

Outcome: The outcome was the test score of the Swedish Scholastic Aptitude Test (SweSAT; we refer to this henceforth as 'the test score'). It is an optional standardized test,[22] which has been an instrument, together with the grade point average (GPA) from upper secondary schools in Sweden, for higher education selection in Sweden. Applicants to higher education are ranked by GPA and/or the test score. There is no restriction on the number of times that one may re-take the test; universities automatically consider an applicant's best test score from the re-takes. Therefore, it is common for applicants to

take the test multiple times. The SweSAT is usually administered twice a year during April and October. Because the level of difficulty varied between tests, raw test scores were normed so that scores from different test occasions were comparable.[23] Since 2011, the test scores are normed to a scale between 0.00-2.00 (with 0.05 increments). We analyzed the normed test scores on its original scale multiplied by 100, yielding test scores ranging between 0-200.

A total of 16 test occasions were included during the follow-up period. We extracted test records for the identified individuals with ADHD and excluded records of incomplete tests from analyses. Age at testing was restricted to between 17 (because students start taking the tests during the second year of upper secondary school) and 30 years. For comparison, we extracted the test scores for population controls who were not diagnosed with ADHD and were matched with each case on sex, birth year, and residential area at the time of the first diagnosis, at a ratio of 10:1.

Exposure: The exposure was ADHD medication. We extracted medication records of stimulants (including methylphenidate, amphetamine and dextroamphetamine) and non-stimulants (atomoxetine) from the Prescribed Drug Register. In line with previous definitions,[24-26] we defined the medicated periods as having two dispensing records with less than 6 months (183 days) apart. The non-medicated periods are thus any period other than those defined medicated periods during the follow-up. We assigned the test dates to the pre-defined medicated/non-medicated periods, to determine the medication status at the testing.

Covariates: In agreement with previous studies,[27,28] we observed significant linear and quadratic effects of age and practice (as measured by the number of previous tests) in association with the test scores, meaning that test scores improve, at a declining rate, as people get older, and as they take more tests. This observation forms the basis of the adjustment in the main analyses using a within-patient design (the effects of covariates are shown in Supplementary Table 1). Other covariates including sex, test year, IQ (measured in Stanine scores) and parents' highest educational level were considered at the cohort level (the estimates are shown in Supplementary Table 2).

Statistical analysis

We first compared the basic characteristics between individuals with ADHD who had taken SweSAT test and their matched population controls, as well as between ADHD individuals with and without medication during study follow-up period.

In the main analyses using the within-patient design, the eligible study subjects were individuals with ADHD who had taken repeated tests and used ADHD medication during the follow-up. We tested the association between medication use and the test scores using a conditional generalized estimation equation (CGEE), conditioning on the individual patient.[29,30] The analyses were performed with and without the adjustment of time-varying confounders including age and the number of previous tests. Because each individual serves as his or her own control in this design, all the time-invariant

confounders were implicitly adjusted for. We also tested the presence of carry-over effects to ensure that the estimates were not biased (Online Supplement).

For comparison, we also conducted analyses at the cohort level, i.e., without controlling for confounding by indication.[31,32] In these analyses, the test scores from all patients during medicated periods were compared with those during non-medicated periods (referred to as 'between-patient comparison'; Online Supplement).

All the analyses were performed in R, using the R package 'drgee' for the GEE and CGEE models.[33]

Sensitivity analyses

To investigate whether the results were sensitive to how the medicated/non-medicated periods had been defined, we also assigned the medication status for each test date according to the number of days since the last dispensing. We reasoned that one is more likely to be taking medication if the test date is closer to the last dispensing, and conversely, less likely to be on medication if there is a large gap in between the last dispensing and the test. The following cutoff values were tested: 1) 6 months (183 days) to define both on and off medication; 2) 3 months (91 days) to define both on and off medication; 3) on medication if the test date was no more than 3 months since the last dispensing, and off medication if the last dispensing and the test date was more than 6 months apart (those with the gap in between 3 to 6 months were

set as missing).

Stimulant ADHD medication might have different efficacy from non-stimulants.[34] To test whether different types of drugs might influence the test scores differently, we identified two groups: stimulant-only users, and non-stimulant/mixed users. The association of medication use and the test scores was assessed within these two groups.

ADHD frequently co-occurs with learning disability (LD), but it has been shown that attention problems in ADHD patients is not limited to its association with LD.[35] However, it is not clear whether the association between ADHD medication and academic outcomes might differ in patients with or without LD. To answer this question, we ran a sensitivity analysis restricting our sample to the subset of individuals with ADHD but without co-existing LD. We identified people with LD either from the National Patient Register (code 315 in ICD-9 and F81 in ICD-10) or from the test records (there is a special test category for individuals with dyslexia).

In order to evaluate whether the association with test scores was specific to ADHD medications, we examined the effect of selective serotonin reuptake inhibitors (SSRI) on the test scores within these individuals with ADHD, both before and after the adjustment of ADHD medication use. Similar to the case of ADHD medications, the dispensing records of SSRI (including fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and escitalopram) were extracted from the Prescribed Drug Register and the medicated and non-

medicated periods of SSRI were defined in the same way.

Results

Approximately 11% of all 61,640 individuals with ADHD diagnosis had taken the test (or 6% if we consider only the tests during the study follow-up). The corresponding percentage in the matched population controls was 32% (or 19% during follow-up).

Individuals with ADHD who had taken the test took significantly fewer tests at a later age as compared to their matched population controls (Table 1). These individuals, however, did not differ from matched controls in the mean value of the test scores, despite scoring slightly lower in IQ. No difference was observed in parents' highest educational levels between test takers with ADHD and matched controls. Of the 3,718 individuals with ADHD who had taken the test, 74% (2,745 patients) received ADHD medication (referred to as the 'medicated group'), while the remaining 26% (973 patients) were not medicated during the entire follow-up period (referred to as the 'never-medicated group'). Notably, the mean value of the test scores was over 10 points higher among the medicated group than among the never-medicated group (94.1 versus 83.5; Table 2).

In the within-patient analysis, we compared the test scores from 930 individuals with repeated tests (2,524 tests) during their own medicated versus non-medicated periods. The use of ADHD medications was associated

with an increase of 13.1-point (95% CI, 9.7 to 16.5, P<0.001) in the test scores. However, the effect was reduced to a 4.8-point increase (95% CI, 2.3 to 7.3, P<0.001; Table 3) after accounting for age and practice effects. That is, among people who had taken multiple tests and used ADHD medications intermittently, the test scores were on average 4.8 points higher (on the scale of 0-200; or 0.048 on the original scale) when the patient was on medication. The estimated improvement in the test scores appeared to be larger, although not significantly different, in males than in females (p-value from testing the interaction term of medication status and sex = 0.31; Table 3).

In the between-patient comparison, we did not find a significant association between the medication use and the test score (Online Supplement).

Sensitivity analyses

Within patients, medication was also linked with higher test scores when we used alternative definitions of medication status at the test date. The estimates of mean difference in the test scores, ranging between 3.6 and 4.0, were highly consistent even when we changed the number of days as different cut-off values (Table 4).

Seventy-two percent of the medicated ADHD group (665 individuals) were stimulant-only users. The association between ADHD stimulants and the test scores was weaker than the association with non-stimulant/mixed drugs, although the estimates were not significantly different (p-value from testing the interaction term of medication status and type of users = 0.23; Table 5). We

identified fewer than 100 individuals with ADHD and coexisting LD; this subset was too small to warrant separate analyses. Instead we examined the association among individuals with ADHD who did not have comorbid LD; the estimated mean test score difference was 5.1 points (95% CI, 2.5 to 7.6) in this subset.

In contrast, we only found a small, non-statistically-significant, improvement in test scores associated with SSRI use, regardless of adjustments for the use of ADHD medication. Within individuals with ADHD who had taken SSRI, there was a 2.4-point difference (95% CI, -0.9 to 5.6; Table 5) in the mean test scores during SSRI-medicated versus non-medicated periods after adjusting for the use of ADHD medication.

Discussion

In this study, we examined the performance of individuals with ADHD at the higher education entrance examinations during their medicated and non-medicated periods. Among the people with a diagnosis of ADHD, the use of ADHD medication was linked with higher scores in the SweSAT, and that this result survived several sensitivity analyses. The size of the effect was 0.048-point improvement on the original scale of the test scores, equivalent to 0.11 standard deviation. Comparing the magnitude of effects on test performance, the benefit from taking ADHD medication was comparable to having one previous test experience (0.12 standard deviation). The effect might be stronger for individuals with average or high performance at the initial test (Online Supplement). Our results corroborate the emerging evidence from randomized clinical trials[36-38] and observational studies[39-41] that the medication is associated with a small improvement in standardised tests or GPA,[18] and further extend the evidence to the age range of adolescence and adulthood which has been particularly understudied.[42]

This effect size, albeit small, approximates to the increment of 0.05 in the normed test scores. Such improvement might translate to a higher rank among test applicants, potentially enhancing the chances of receiving higher education. The current results, therefore, might have implication on one's educational attainment. In addition, educational level has been shown as a strong predictor of occupational outcomes in adult ADHD patients;[43] thus, the resultant better education might lead to other long-term implications. We note,

however, the small effect size suggested that other treatment programs are needed to help support individuals with ADHD in educational settings.

In the within-patient design, confounders that are constant within individuals, such as genetic make-up for disease severity, intelligence and conscientiousness, or family and school environment that stimulate learning (e.g., receiving special educational services), are implicitly adjusted for. We adjusted for age and practice effects to address the confounding of increased test scores at repeated tests due to natural curve of improvement in ADHD symptoms[44] and improvement in test taking ability. In addition, we did not find evidence for exposure-outcome carry-over effects (Online Supplement). This suggests that the association between ADHD medication use and the test scores after controlling for age and practice effects is relatively robust. However, unmeasured confounders that vary within individuals might still be present (e.g., periods of time when individuals decide to take medication might represent time when they make other health and life decisions that may enhance test performance), for which we tested the association of the test scores with SSRI, the next commonly used medication in individuals with ADHD. No statistically-significant association was detected between SSRI use and the test scores, indicating limited impact of such unmeasured factors (a further discussion in, Online Supplement). Yet, as in all observational studies we are unable to rule out all time-varying confounds.

Compared to many studies that used retrospective parental reports on medication use,[40] we inferred medication use during the test periods from

medication prescription records. Thus, our results were not affected by any recall bias. The results, however, rely on whether the medication uses were correctly assigned. Using an alternative definition where we traced the test date back to the closest drug dispensing and counted the number of days in between, we demonstrated that the observed association was not sensitive to the definition of medication exposure. But, there is still uncertainty about medication status on the test date. Previous studies have shown that ADHD treatment non-compliance was found to be the norm rather than the exception.[19] In the cases where treatment non-compliance occurred during our defined medication periods, our estimation was likely to be conservative rather than an overestimate of the true medication effect.

Because higher education entrance examinations comparable to the SweSAT exist in most countries, our results of a positive association between medication use and these tests within individuals with ADHD may generalise to some countries with a similar prevalence of ADHD medication use. We note the likelihood of some self-selection in our study. First, the proportion of individuals who had taken SweSAT tests was nearly three times higher in the population controls than in the individuals with ADHD, probably due to a higher percentage of school drop-outs[45] and of individuals who had chosen other educational tracks, such as vocational education and training in the ADHD group. Further selection arose from the within-individual design which restricted to the individuals who had taken repeated tests. Second, IQ among the individuals with ADHD who had taken the tests were comparable to IQ among the matched controls, suggesting that our results might be specific to

the individuals with normal cognitive function. This might contribute to the observation of a similar mean test scores among individuals with ADHD and the matched controls, even though we might have expected people with ADHD diagnoses to have scored more poorly. We were unable to test whether the identified link between ADHD medication and improved test performance also applies to individuals with more impaired cognitive function or other severe functional impairment. However, it has been suggested that the individuals with the greatest deficit are the ones who experience the most benefit from ADHD medication.[46,47] We, therefore, conjecture that the identified link might apply to the full spectrum of functioning in people with ADHD. It is important to note, however, by probing the link we explicitly do not assume causality.

ADHD medications had almost 50% increase in prescriptions dispensed in the US from 2002 to 2010.[48] Evidence on links between medication and outcomes is an essential part of dispensing decisions. Like all medications, ADHD medications have unwanted effects[16,49] including concerns regarding non-serious adverse events, such as decreased appetite and sleep problems, and the possibility of serious adverse events,[15,50,51] which need to be considered. However, this study suggests that ADHD medications may help improve performance on an important achievement test and, thus, enhance the educational attainment of people with ADHD.

Conclusions:

For the people with a diagnosis of ADHD, the use of ADHD medication is associated with better performance at the higher education entrance tests. This evidence should be considered together with the current list of risks and benefits of ADHD medication to guide clinical decisions.

Tables

Table 1. Basic characteristics of individuals with ADHD who had taken SweSAT test as compared to their matched population controls.

	ADHD patients (n=3718)	Matched controls (n=8371)[1]	Test of group differences[2]
Average number of tests per person (s.d.)	1.58 (1.09)	1.74 (1.20)	<0.001
Mean age at test (s.d.)	22.10 (3.30)	20.55 (2.44)	<0.001
Mean test score (s.d.)	91.40 (46.16)	90.51 (43.02)	0.20
Mean IQ in stanine scores (s.d.)[3]	5.62 (1.82)	5.86 (1.74)	0.002
Father's highest education, over 12 years of education (%)	44.75%	46.12%	0.17
Mother's highest education, over 12 years of education (%)	53.42%	53.19%	0.83

1. Population controls were matched with each ADHD patient on sex, birth year and residential area at the time of diagnosis, at a ratio of 10:1. 8371 individuals from 37180 matched controls had taken test during the study follow-up.
2. Two-sided t tests were used for continuous variables. Chi-square tests were used for 2-by-2 contingency table, with Yates' correction.
3. Based on 20% non-missing IQ data in males.

Table 2. Basic characteristics of ADHD individuals with and without medication during study follow-up period.

	Medicated ADHD group (n=2745)	Never-medicated ADHD group (n=973)	Test of group differences[1]
Male (%)	50.49%	56.22%	0.002
Average number of tests per person (s.d.)	1.58 (1.08)	1.53 (0.89)	0.18
Mean age at test (s.d.)	22.26 (3.36)	21.63 (3.08)	<0.001
Mean test score (s.d.)	94.12 (46.13)	83.46 (45.32)	<0.001
Mean IQ in stanine scores (s.d.)[2]	5.69 (1.86)	5.41 (1.71)	0.08
Father's highest education, over 12 years of education (%)	45.69%	42.06%	0.06
Mother's highest education, over 12 years of education (%)	54.92%	49.12%	0.002

1. Two-sided t tests were used for continuous variables. Chi-square tests were used for 2-by-2 contingency table, with Yates' correction.
2. Based on about 20% non-missing IQ data in males.

Table 3. Associations between ADHD medication and SweSAT test scores, using definition of medicated/non-medicated periods.

	Within-patient comparison[1]			
	N patients	N tests (On/Off)[2]	Mean test score difference (95% CI)	P
Male	493	1364 (325/1039)	5.69 (2.14, 9.23)	0.002
Female	437	1160 (355/805)	3.60 (0.06, 7.14)	0.05
Overall	930	2524 (680/1844)	4.80 (2.26, 7.34)	<0.001

1. In the within-patient comparison, the test scores during medicated periods were compared with non-medicated periods in the same individual, after adjusting for both linear and quadratic effects of age and the number of previous tests. The analyses were based on individuals with repeated tests.
2. Total number of tests and the number of tests during medicated versus non-medicated periods in brackets. All possible combinations of medication use were allowed.

Table 4. Associations between ADHD medication and SweSAT test scores, using days from last dispense to define medication status at test date.

	6 months as cutoff		*3 months as cutoff*		*Less than 3 months as ON, more than 6 months as OFF*	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Male	4.80 (1.61, 7.98)	0.003	4.05 (0.90, 7.19)	0.01	4.83 (1.28, 8.39)	0.007
Female	2.46 (-1.41, 6.33)	0.21	2.95 (-0.30, 6.21)	0.08	3.00 (-1.06, 7.05)	0.15
Overall	3.72 (1.26, 6.19)	0.003	3.56 (1.28, 5.84)	0.002	4.02 (1.34, 6.69)	0.003

Estimates of medication effect (i.e., estimated mean difference in the test scores while one was on medication versus off medication) were from within-patient analysis, adjusted for both linear and quadratic effects of age and the number of previous tests. The number of patients and tests were the same as in Table 3 (within-patient level).

Table 5. Associations between ADHD medication and SweSAT test scores, in sensitivity analyses.

Types of cohort, medication	N	N tests	Mean test score difference (95% CI)	P
ADHD diagnosed in the National Patient Register				
Within stimulant-only users	665	1816	3.81 (0.94, 6.69)	0.009
Within non-stimulant/mixed users	265	708	6.93 (1.81, 12.05)	0.008
Within patients without co-existing LD	844	2264	5.05 (2.47, 7.62)	<0.001
SSRI use and test scores (not adjusted for ADHD medication)	556	1475	2.71 (-0.57, 5.99)	0.11
SSRI use and test scores (adjusted for ADHD medication)	445	1207	2.37 (-0.88, 5.63)	0.15

Estimates of medication effect (i.e., estimated mean difference in the test scores during medicated periods compared to non-medicated periods) were from within-patient analysis, adjusting for both linear and quadratic effects of age and the number of previous tests.

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Dr Lu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

H. Larsson has served as a speaker for Eli-Lilly and Shire and has received a research grant from Shire; P. Lichtenstein has served as a speaker for Medice all outside the submitted work.

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Online Supplement

Association between medication use and the performance of higher education entrance tests in individuals with attention deficit-hyperactivity disorder

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Testing carry-over effect:

The within-patient design assumes that there is no carry-over effect between exposures and outcomes for the same individual.[1] Carry-over effects, in this context, can take place in many forms, with some more plausible than others: for example, medication use at an earlier test can influence the decision of medication use ("exposure-to-exposure"), or more directly influence the scores ("exposure-to-outcome"), at the following test(s); or, an individual's scores at earlier tests can influence his or her scores ("outcome-to-outcome") or medication use ("outcome-to-exposure") at later test(s). Except for the first form (i.e., earlier medication use influence later use), these carry-over effects, if exist but are not accounted for, will lead to bias in the estimates from these models.[1] Therefore, we adjusted for the age and practice effects, both linear and quadratic terms, to account for the outcome-to-outcome carry-over. In addition, we tested the presence of the other two forms of carry-over, by fitting the specific paths into the model. To test whether the exposure-to-outcome carry-over exists, we examined the association of current test scores with the medication use at earlier tests, while adjusting for an indicator of the first test (because no information on the prior medication use), current medication use, as well as the age and practice effects. Similarly, to test whether the outcome-to-exposure carry-over exist, we examined the association of current medication use with previous test scores, while adjusting for an indicator of first test, current test scores, as well as age and practice effects.

There was no evidence suggesting that the exposure-outcome carry-over effects exist. The effect of previous medication use on the current test score was not significantly different from 0 (-0.74 to 4.03), neither was the odds ratio of previous test score on the use of current medication different from 1 (0.99 to 1.03). These results suggest that the association between ADHD medication and test scores after controlling for the learning effect is not biased by other types of carry-over effects.

Between-patient comparison:

For comparison with results from the within-individual analysis, we also conducted analyses at the cohort level, i.e., the test scores from all patients during medicated periods were compared with those during non-medicated periods (referred to as 'between-patient comparison'); thus there was no restriction on study subjects. We used generalized estimation equation models to examine the associations between the use of ADHD medication and the test scores from all patients, with robust standard errors accounting for the correlated test scores from the same patients. The between-patient comparison was adjusted for age, sex, number of previous tests, test year, parental education level and IQ.

In the between-patient comparison when confounding by indication was not controlled for, we did not find a significant association between the medication use and the test score. For all individuals in the medicated ADHD group, the estimated mean difference in the test scores was 1.2 (95% CI, -2.4 to 4.8) comparing all medicated periods with non-medicated periods.

	Between-patient comparison[1]			
	N patients	N tests (On/Off)[2]	Mean test score difference (95% CI)	P
Male	1386	2257 (570/1687)	-0.63 **(**-5.56, 4.30**)**	0.80
Female	1359	2082 (602/1480)	2.67 (-2.55, 7.90)	0.32
Overall	2745	4339 (1172/3167)	1.23 (-2.38, 4.83)[3]	0.51

1. In the between-patient comparison, the test scores from all individuals during medicated periods were compared with those during non-medicated periods, after adjusting for both linear and quadratic effects of age and the number of previous tests, test year, parents' highest education level (whether or not had over 12 years of education), and sex in the overall analysis. The presented results were not adjusted for IQ due to large percentage of missing data.
2. Total number of tests and the number of tests during medicated versus non-medicated periods in brackets. All possible combinations of medication use were allowed.
3. The mean test score difference in the between-patient comparison was -1.02, 95% CI was -9.29 to 7.24 after adjusting for IQ.

The concomitant use of SSRI:

The concomitant use of SSRI appeared to be more prevalent during ADHD medicated periods compared to non-medicated periods (see the table below). We note that the non-significant improvement in test scores associated with SSRI, approximately 0.06 standard deviation of the test scores, was less likely to indicate a general effect related to medication pattern; instead, it was perhaps driven by the subset of individuals with ADHD and coexisting depression (within individuals with both ADHD and depression who had taken repeated tests, the estimated mean difference in the test scores due to SSRI was twice as large as the estimate from individuals with ADHD only, after adjusting for ADHD medication use; results not shown). This observation reflects previous findings that SSRI use is associated with improving attention and remaining executive function in patients with depression.[2]

	ADHD medication periods	
	1844 OFF periods	680 ON periods
Intermittent use of SSRI; number (%)		
OFF	734 (39.8%)	250 (36.8%)
ON	142 (7.7%)	81 (11.9%)
Never-treated	968 (52.5%)	349 (51.3%)

Stratifying subjects by test performance:

In this sensitivity analysis, we aimed to test whether the association between ADHD medication and test scores differed among individuals with different test performance. We indirectly investigated this question by ranking subjects according to the scores from their first tests: those within the bottom 20% were considered as 'low' performance group, within top 20% were considered as 'high' performance group and the remaining ones were 'average' performance group. It should be noted that this represents a crude way of stratifying subjects, because scores at different test occasions which might have a varying level of difficulties were pooled together. We then performed within-individual analyses in each of these three groups. The results are shown below:

	N individuals	**N tests**	**Mean test score difference (95% CI)**	**P**
Low performance group (scores from the first test below 50)	192	512	0.36 (-5.06, 5.78)	0.90
Average performance group (scores from the first test between 50 to 130)	555	1501	5.67 (2.69, 8.65)	0.0002
High performance group (scores from the first test above 130)	183	511	7.80 (2.32, 13.27)	0.005

There was no evidence for a medication effect among the low performance group. The medication effect appeared to be the strongest in the high performance group, but its wide confidence interval (CI) completely overlapped with the CI from the average performance group.

Supplementary Table 1. The effect of adjustments at the within-patient comparison.

Variables	Effect	S.E.	P-value
Age	15.49	3.36	4E-06
age^2	-0.28	0.07	8E-05
previous number of tests	5.86	0.73	1E-15
previous number of tests^2	-0.19	0.11	8E-02

Supplementary Table 2. The effect of adjustments at the between-patient comparison.

Variables	Effect	S.E.	P-value
Age	-5.93	3.46	0.087
age^2	0.17	0.07	0.022
previous number of tests	13.77	1.23	< 2e-16
previous number of tests^2	-0.87	0.22	6E-05
test year 2007	-5.64	3.05	0.0641
test year 2008	-8.43	3.45	0.0145
test year 2009	-9.46	3.23	0.0034
test year 2010	-11.51	3.26	0.0004
test year 2011	-12.59	3.24	0.0001
test year 2012	-14.91	3.16	2E-06
test year 2013	-18.35	3.15	6E-09
sex_female	-13.08	1.80	4E-13
Father's highest education; over 12 years of education	12.58	1.92	6E-11
Mother's highest education; over 12 years of education	14.32	1.97	4E-13

* IQ had an effect of 12.05 (s.e.=2.27, P=1e-7; and the effect of mother's highest education was reduced to 2.77, s.e.=5.80, P=0.63) in the adjusted model that was based on 20% non-missing data in males.

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