Supplementary Online Content

Lu Y, Sjölander A, Cederlöf M, et al. Association between medication use and performance on higher education entrance tests in individuals with attention-deficit/hyperactivity disorder. *JAMA Psychiatry.* Published online June 28, 2017. doi:10.1001/jamapsychiatry.2017.1472

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

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 (eTable 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 in eTable 4.

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.

The concomitant use of SSRI:

The concomitant use of SSRI appeared to be more prevalent during ADHD medicated periods compared to non-medicated periods (eTable 5). 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]

eTable 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

eTable 2. The Effect of Adjustments at the Between-Patient Comparison

Variables	Effect	S.E.	*P* Value
Age	-5.93	3.46	.09
age^2	0.17	0.07	.02
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	.06
test year 2008	-8.43	3.45	.01
test year 2009	-9.46	3.23	.003
test year 2010	-11.51	3.26	<.001
test year 2011	-12.59	3.24	<.001
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*=.63) in the adjusted model that was based on 20% non-missing data in males.

eTable 3. Associations Between ADHD Medication Use and SweSAT Scores in Between-Patient Comparison

	Between-patient comparison[1]			
	N patients	N tests (On/Off)[2]	Mean test score difference (95% CI)	*P* Value
Male	1386	2257 (570/1687)	-0.63 **(**-5.56, 4.30**)**	.80
Female	1359	2082 (602/1480)	2.67 (-2.55, 7.90)	.32
Overall	2745	4339 (1172/3167)	1.23 (-2.38, 4.83)[3]	.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.

eTable 4. Associations Between ADHD Medication Use and SweSAT Scores in Within-Patient Comparison, Stratified by Performance on the Initial Test

	N individuals	N tests	Mean test score difference (95% CI)	*P* Value
Low performance group (scores from the first test below 50)	192	512	0.36 (-5.06, 5.78)	.90
Average performance group (scores from the first test between 50 to 130)	555	1501	5.67 (2.69, 8.65)	.0002
High performance group (scores from the first test above 130)	183	511	7.80 (2.32, 13.27)	.005

eTable 5. Pattern of concomitant use of SSRIs

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

eReferences

1. Sjolander, A., Frisell, T., Kuja-Halkola, R., Oberg, S. & Zetterqvist, J. Carry-over effects in sibling comparison designs. *Epidemiology* (2016).
2. Herrera-Guzman, I. *et al.* Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on attention and executive functions in patients with major depressive disorder. *Psychiatry Res* **177**, 323-9 (2010).