Supplemental Content

eAppendix 1: Sensitivity and negative control analyses

Several sensitivity analyses were planned to test the validity and robustness of the initial study results.

1) Alternative analyses were conducted based on different drug non-adherence scenarios. Each exposed period was further extended by adding 1 to 10 weeks after the end of an exposed period to assess this effect.

2) Analyses were re-run excluding patients documented as having a febrile seizures (ICD-9-CM: 780·31, 780·32) before the observation period.

3) As the period before ADHD diagnosis may have had less medical attention, we re-ran the analysis by redefining the start of observation period to January 1, 2001, the sixth birthday of the patient, the first observed date of ADHD diagnosis, or the first date of methylphenidate treatment, whichever occurred last.

4) Patients with MPH exposure before the start of the observation period were removed from the analyses. As the self-controlled case series compared the incidence within an individual, included individuals were not necessary to be incident users of MPH. This will access this potential effect.

5) Additional analyses were conducted on a subset of patients with more than 120 days of MPH exposure in order to test the effects of more prolonged medication exposure.

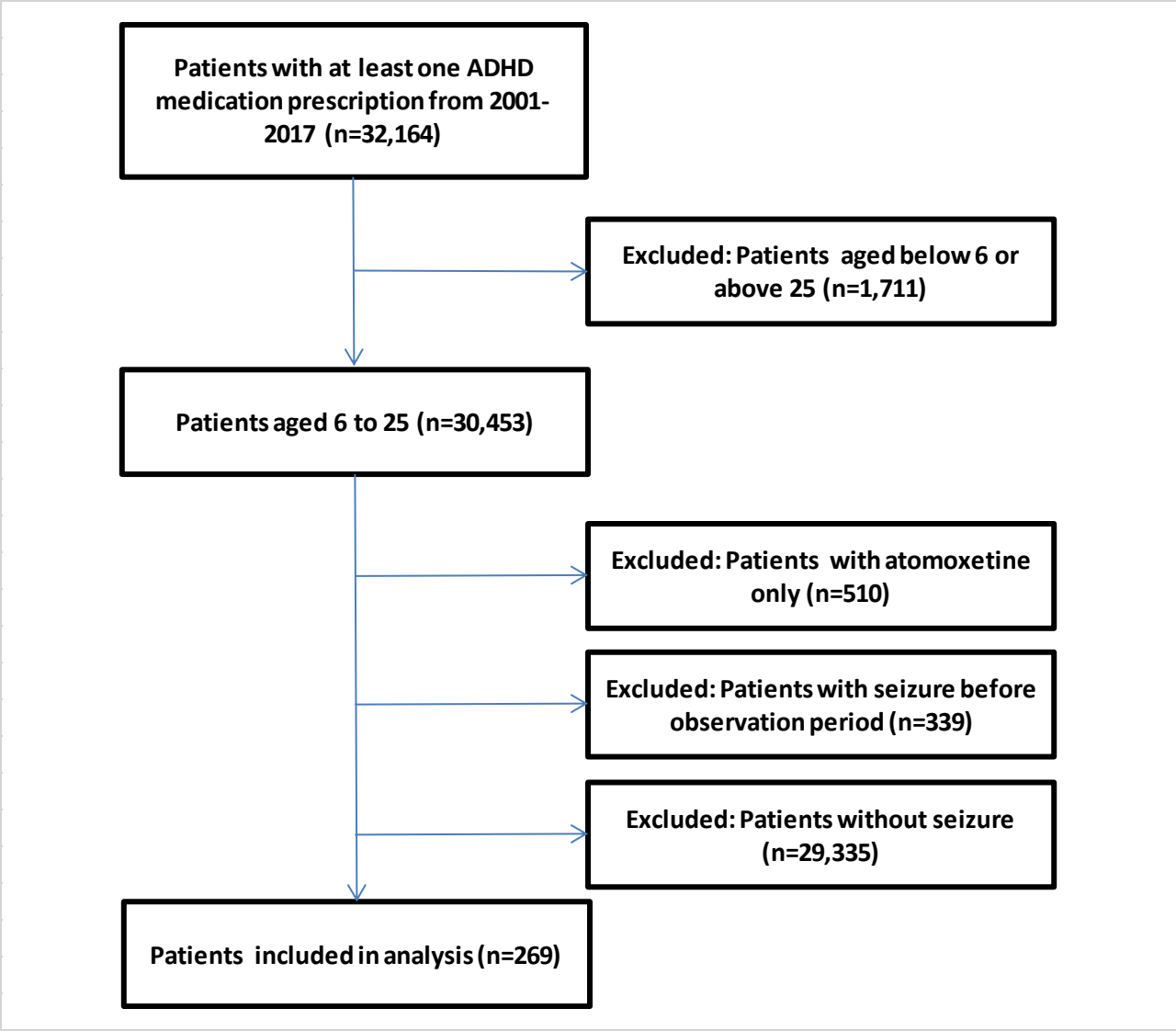
6) We conducted a negative control analysis to validate the use of skin infection as an alternative outcome (ICD-9-CM: 680-686). To our knowledge, there is no published evidence or pharmacologic/biological hypothesis to support MPH is associated to skin infection. If association was found in this analysis, it would raise the possibility that our study design is prone to bias. We used the same setting and methods in the negative control analysis.

7) Although between-individual confounding will not affect our results as we have applied the self-controlled case series design, we recognised that we cannot exclude the possibility of time-variant unmeasured confounding factors. To further assess the potential impact of any unmeasured confounding on our result, we conducted a sensitivity analysis by computing the E-value.[1,2] It is defined as the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome, conditional on the measured covariates, to explain

away an observed association.[1,2] E-values is a validated approach that has been widely used to assess the potential effects of unmeasured confounding in observational studies.[3,4]

References:

1. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017; **167**(4): 268-74.
2. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. *Jama-J Am Med Assoc* 2019; **321**(6): 602-3.
3. Ding P, VanderWeele TJ. Sensitivity Analysis Without Assumptions (vol 27, pg 368, 2016). *Epidemiology* 2018; **29**(3): E19-E.
4. Fisher DP, Johnson E, Haneuse S. Association Between Bariatric Surgery and Macrovascular Disease Outcomes in Patients With Type 2 Diabetes and Severe Obesity (vol 32, pg 1570, 2018). *Jama-J Am Med Assoc* 2018; **320**(22): 2381-.

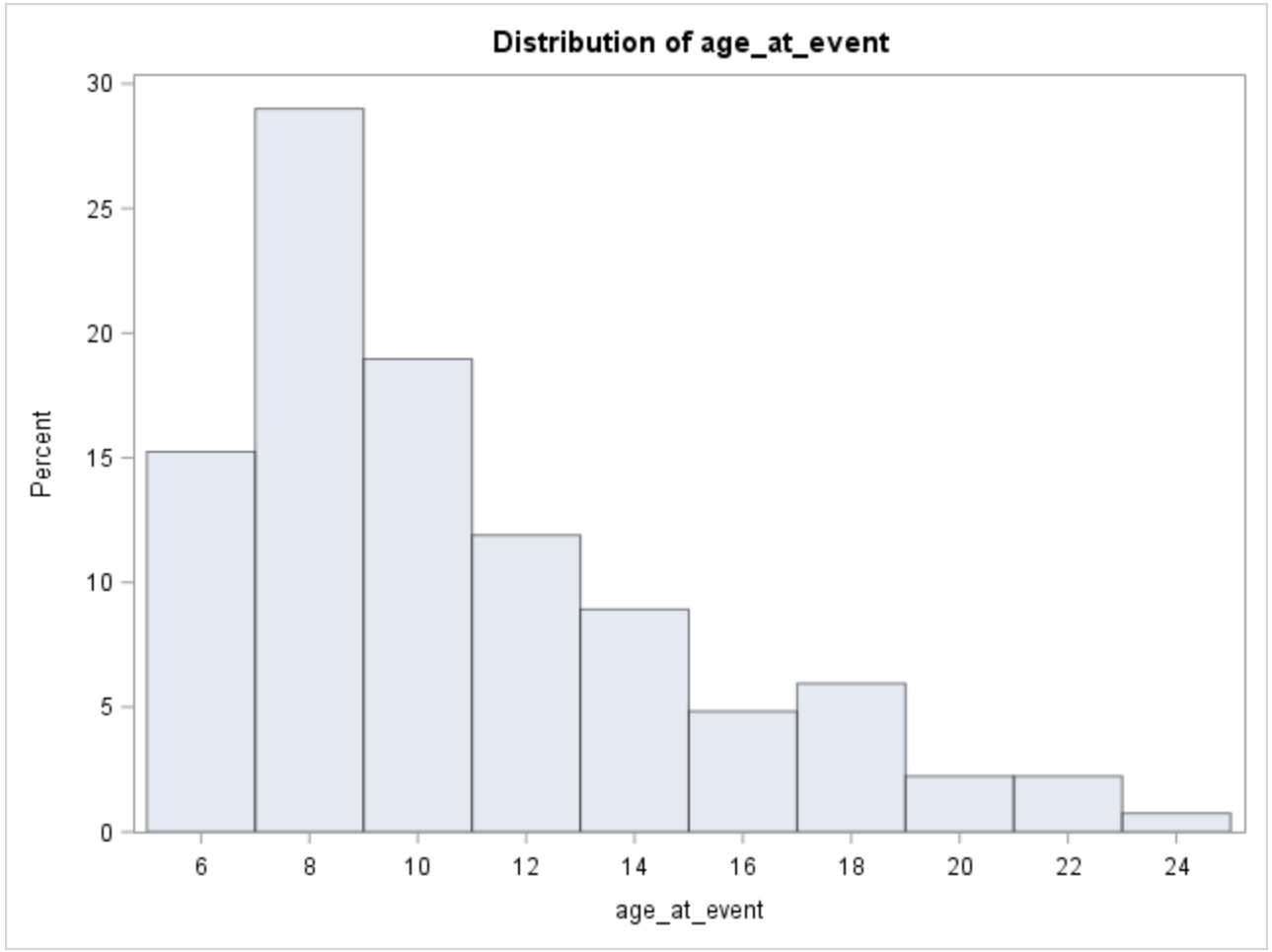


eFigure 1: Flowchart of Patient Identification

eTable 1: Psychiatric co-morbidities of patients with seizure

Condition	ICD-9-CM[a]	Number of Patients (n=269)	(%)	Number of patients with ADHD (n=157)	(%)
Acute reaction to stress	308	13	4·8	8	5·1
Adjustment disorder	309	8	3·0	6	3·8
Anxiety disorder	293·84, 300	9	3·3	6	3·8
Autism spectrum disorder	299	95	35·3	30	19·1
Depressive disorder	296·2, 296·3, 311	<5	<2	0	0
Disturbance of conduct not elsewhere classified	312	10	3·7	7	4·5
Disturbance of emotion	313	25	9·3	16	10·2
Intellectual Disabilities	317-319	80	29·7	30	19·1
Specific delays in development	315	47	17·5	32	20·4
Other psychiatric co-morbidities[b]	290-319	177	65·8	157	100

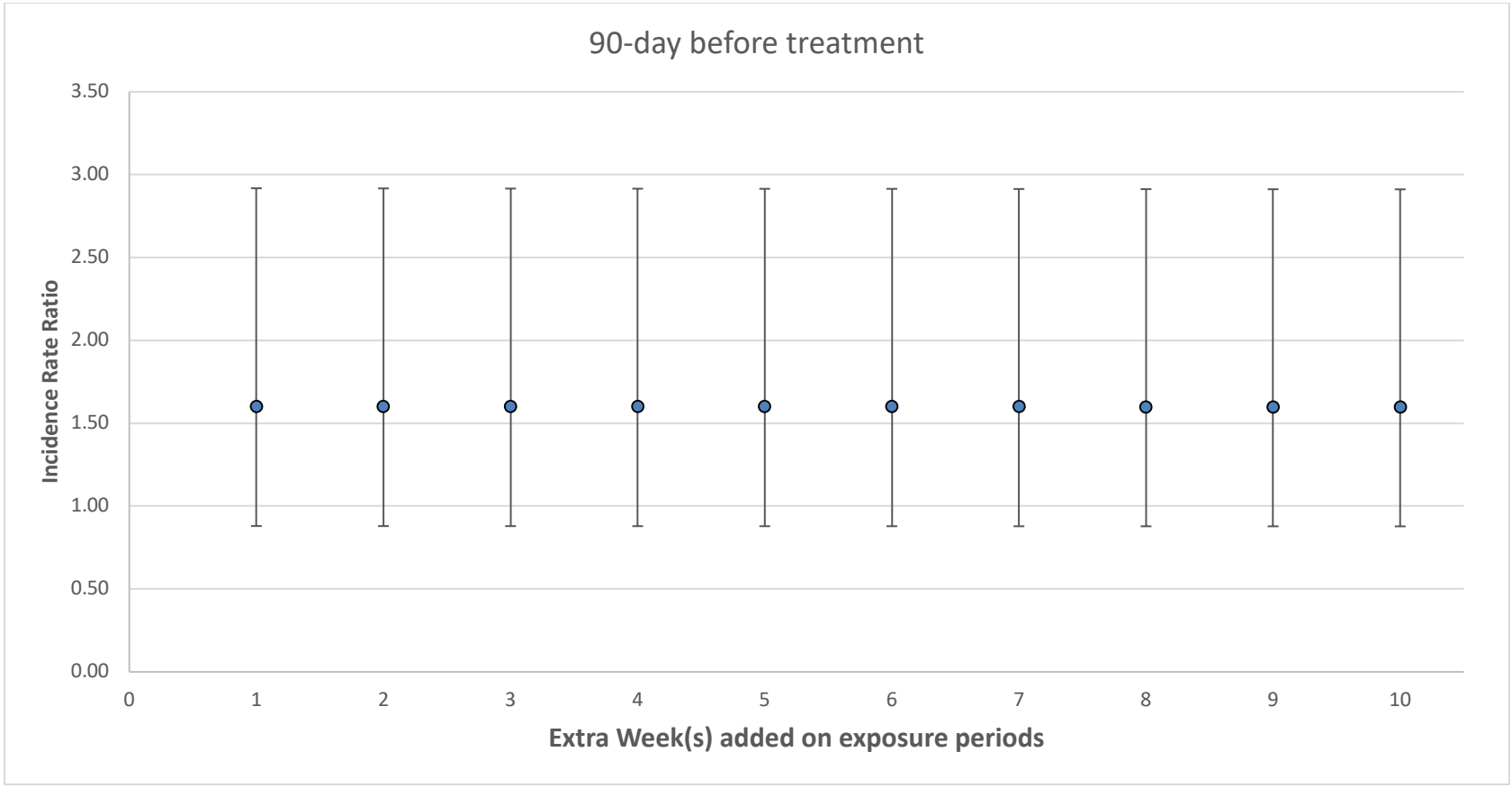
[a]ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification
[b]Other psychiatric co-morbidities included all other disorders from ICD-9-CM code 290-319 which were not listed above



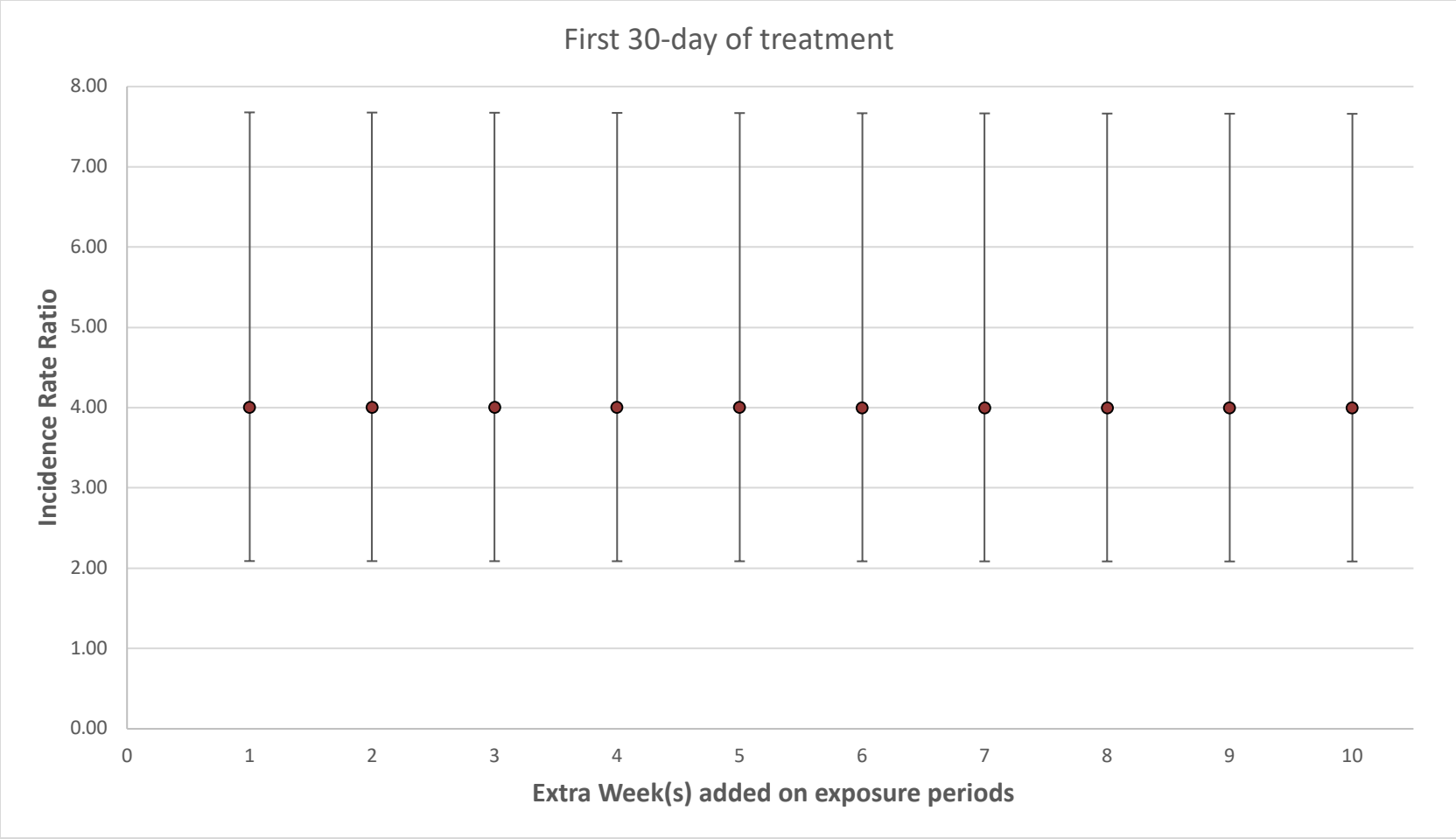
eFigure 2: Histogram of age at the incident seizure

eTable 2: Result of age and gender stratified analyses

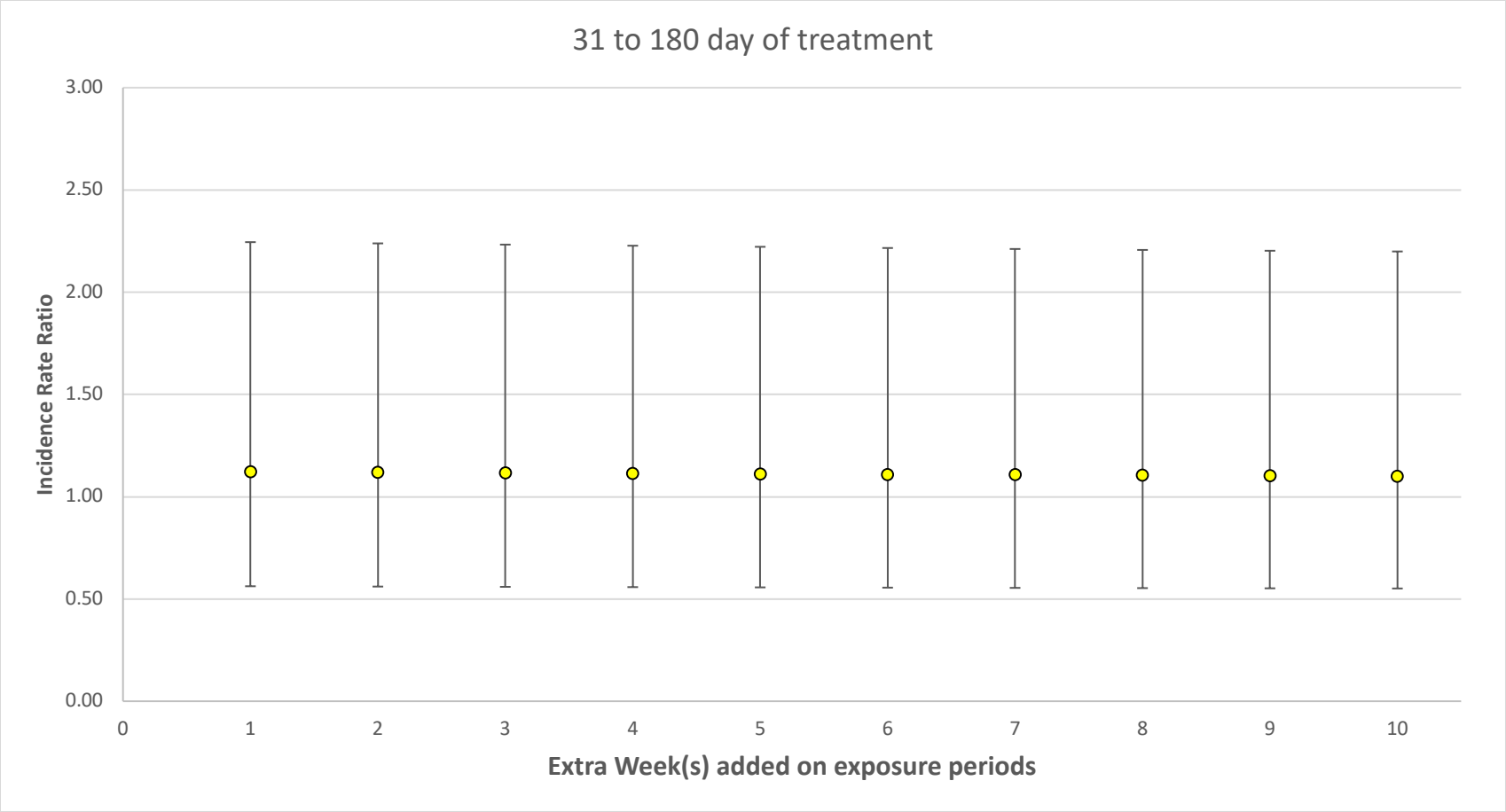
	IRR	95%CI		p-value	IRR	95%CI		p-value	p-value for difference
Gender	Male (n=199)				Female (n=70)				
90-day before treatment	1·71	0·86	3·42	0·13	1·41	0·42	4·70	0·58	0·80
First 30-day of treatment	5·01	2·51	10·00	<0·01	1·43	0·19	10·76	0·73	0·26
31 to 180 days of treatment	0·69	0·25	1·90	0·47	2·25	0·82	6·20	0·12	0·11
Subsequent MPH treatment	1·49	0·95	2·35	0·08	0·96	0·37	2·52	0·93	0·42
Age	Age 12 or above (n=89)				Age below 12 (n=180)				
90-day before treatment	2·19	0·51	9·48	0·29	1·46	0·75	2·86	0·26	0·66
First 30-day of treatment	6·22	1·45	26·70	0·01	3·67	1·75	7·67	<0·01	0·56
31 to 180 days of treatment	3·28	0·94	11·38	0·06	0·84	0·36	1·96	0·68	0·10
Subsequent MPH treatment	1·87	0·81	4·31	0·14	1·32	0·76	2·28	0·32	0·52



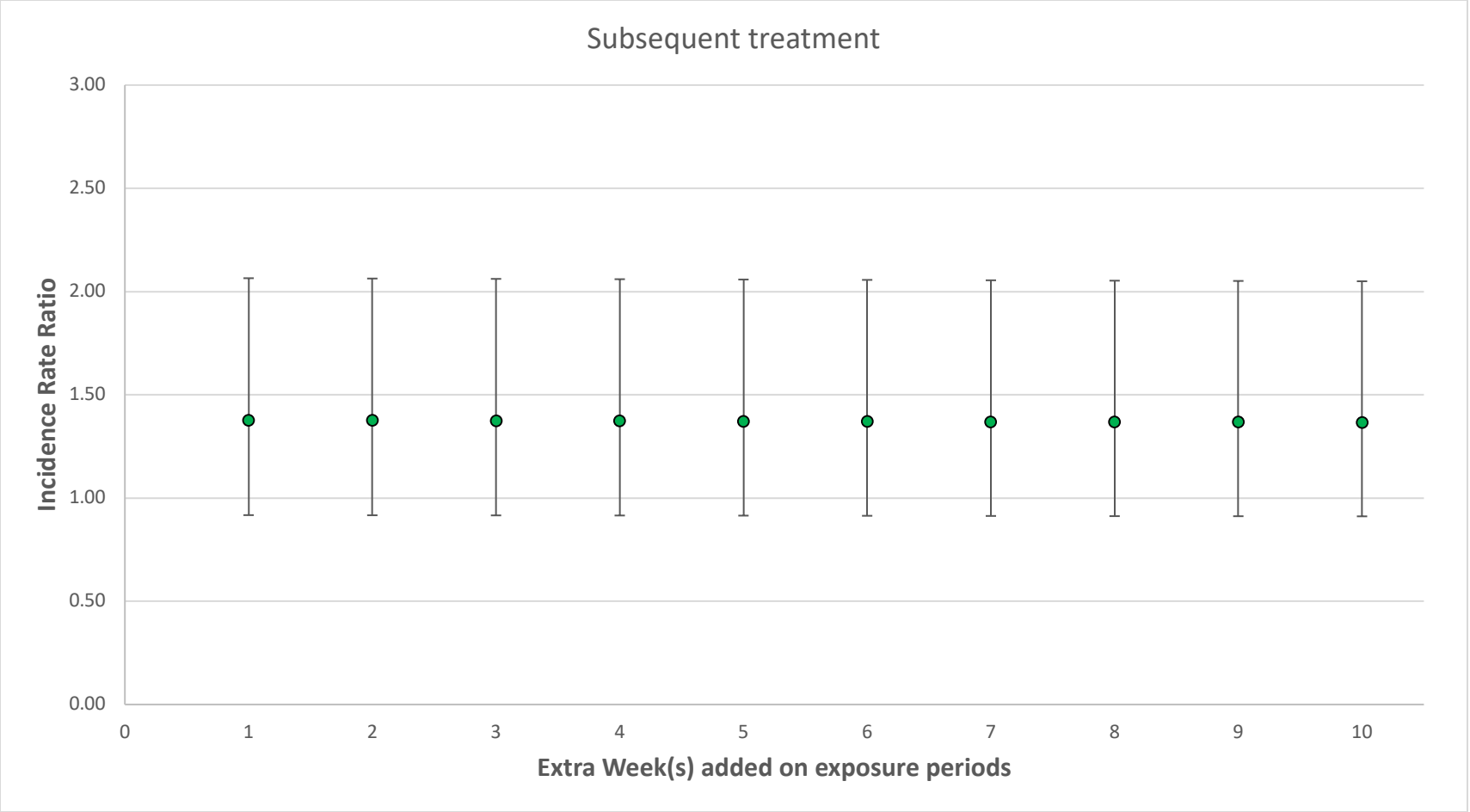
eFigure 3: Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio (IRR) of suicide attempt in the 90-day pre-exposure period



eFigure 4: Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio (IRR) of suicide attempt in the first 30-days MPH exposure period



eFigure 5: Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio (IRR) of suicide attempt in the first 31 to 180 days MPH exposure period



eFigure 6: Sensitivity analysis on exposure periods by adding 1 to 10 weeks after the end of an exposed period: Incidence rate ratio (IRR) of suicide attempt in MPH treatment after the first 180 day

eTable 3 Results from sensitivity analyses

Treatment	Risk window	Number of events	Patient-years	Crude incidence (in 100 patient-year)	IRR*	95%CI		p-value
Sensitivity analysis 2): Without febrile seizure before and during the study period (n=164)								
MPH	90-day before treatment	8	37·97	21·07	1·68	0·80	3·51	0·17
	First 30-day of treatment	6	12·61	47·57	3·74	1·61	8·70	<0·01
	31 to 180 day of treatment	9	40·90	22·01	1·75	0·85	3·59	0·13
	Subsequent treatment	26	297·39	8·74	1·28	0·74	2·22	0·37
	No MPH	115	1338·18	8·59	1·00	1·00	1·00	--
Sensitivity analysis 3): Study start at ADHD diagnosis or first MPH treatment (n=211)								
MPH	90-day before treatment	8	35·29	22·67	1·79	0·84	3·81	0·13
	First 30-day of treatment	10	16·27	61·45	3·77	1·92	7·43	<0·01
	31 to 180 day of treatment	9	51·79	17·38	1·08	0·52	2·23	0·84
	Subsequent treatment	50	386·41	12·94	1·48	0·95	2·30	0·08
	No MPH	134	1605·06	8·35	1·00	1·00	1·00	--
Sensitivity analysis 4): Incident user of MPH treatment (n=253)								
MPH	90-day before treatment	12	62·02	19·35	1·55	0·85	2·82	0·15
	First 30-day of treatment	9	19·36	46·50	3·79	1·91	7·51	<0·01
	31 to 180 day of treatment	7	62·97	11·12	0·93	0·43	2·01	0·85
	Subsequent treatment	43	457·48	9·40	1·25	0·82	1·91	0·29
	No MPH	182	2104·18	8·65	1·00	1·00	1·00	--
Sensitivity analysis 5): At least 120 days of MPH treatment (n=245)								
MPH	90-day before treatment	10	57·39	17·43	1·37	0·71	2·63	0·35
	First 30-day of treatment	6	19·37	30·98	2·36	1·03	5·40	0·04
	31 to 180 day of treatment	8	67·29	11·89	0·93	0·45	1·93	0·84
	Subsequent treatment	50	500·46	9·99	1·27	0·84	1·90	0·26

No MPH	171	1964·87	8·70	1·00	1·00	1·00	--

AD=Antidepressants
AP=Antipsychotics
MPH=Methylphenidate
IRR=Incidence rate ratio
CI=Confidence interval
*All estimates are adjusted for age in 1-year age-band, seasonal effect and other psychotropic medications

eAppendix 2: Results from E-value analyses

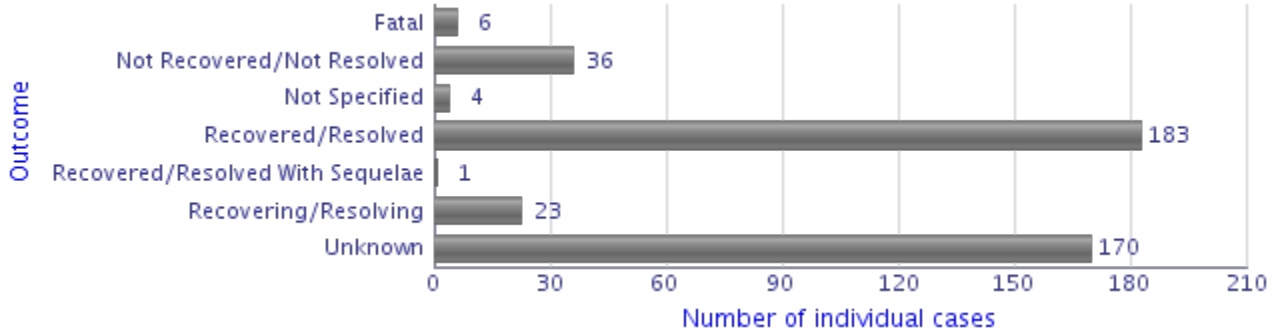
In our study, the IRR for seizure with the first 30-day of MPH treatment was 4·01 with a 95% confidence interval of 2·09 to 7·68. The E-value for the result point estimate was 7·48 with the lower confidence interval was 3·60 in an IRR scale. This result indicates that our observed 4-fold increase in the seizure risk during the first 30-day of MPH could be explained away by an unmeasured time-varying confounder that was associated with both the treatment and the outcome by a risk ratio of 7·48-fold each, above and beyond the confounders that were addressed, but weaker confounding could not do so; the confidence interval could be moved to include 1·00 (i.e. no association) by an unmeasured time-varying confounder that was associated with both the treatment and the outcome by a risk ratio of 3·60-fold each, above and beyond the confounders that were addressed, but weaker confounding could not do so.

It is unlikely that an unmeasured time-varying confounder with this large magnitude of an association with both receiving MPH and risk of seizure exists, as such magnitude is much larger than those risk factors for seizures, in particular concurrent psychotropic medications, for which we have already controlled for in the analyses. Therefore, our result is unlikely to have been due to an unmeasured time-varying confounder and this further supports the validity of our result.

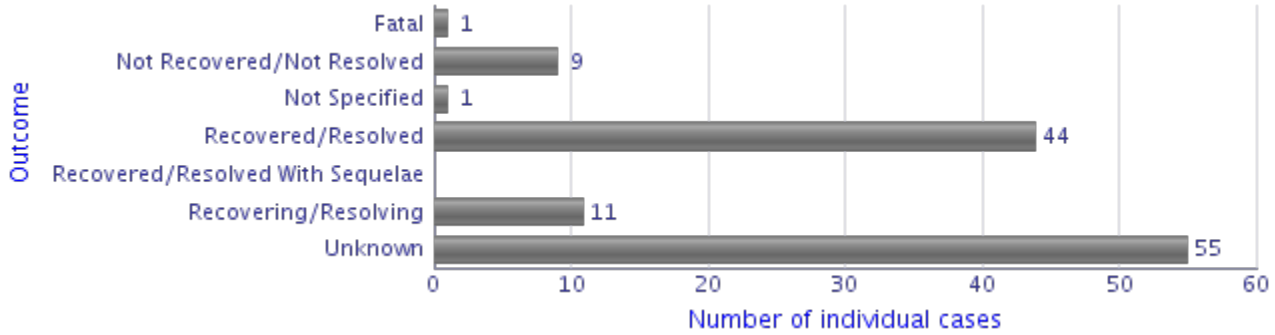
eTable 4: Recurrent seizures in Patients with their incident seizure occurred during MPH treatment

Combination of drugs	Number events	patient-time (days)	patient-time (years)	Crude incidence (in 100 patient-year)
n=11				
With MPH (Subsequent MPH treatment)				
MPH only	7	7431	20·34	34·41
MPH + AD	0	308	0·84	0·00
MPH + AP	0	170	0·47	0·00
MPH + AP + AD	1	50	0·14	730·50
Without MPH				
AD only	0	24	0·07	0·00
AP + AD	0	197	0·54	0·00
AP only	0	6316	17·29	0·00
No medication	3	19376	53·05	5·66

eFigure 7: Seizure and Epilepsy related adverse drug reaction reports for Methylphenidate in EudraVigilance* database



eFigure 7a: Outcomes reported for Seizure cases



eFigure 7b: Outcomes reported for Epilepsy cases

*Reports are publicly available at http://www.adrreports.eu/en/search_subst.html#

eTable 5: Post-hoc analysis adjusted for antiepileptic drugs and benzodiazepines

Treatment	Risk window	IRR*	95%CI		p-value
MPH	90-day before treatment	1·55	0·85	2·81	0·15
	First 30-day of treatment	3·90	2·04	7·48	<0·0001
	31 to 180 day of treatment	1·10	0·55	2·20	0·78
	Subsequent treatment	1·35	0·90	2·02	0·15
	No MPH	1·00	1·00	1·00	--

MPH=Methylphenidate
IRR=Incidence rate ratio
CI=Confidence interval
*All estimates are adjusted for age in 1-year age-band, seasonal effect and other psychotropic medications (antidepressants, antipsychotics, antiepileptic drugs and benzodiazepines)