Title: Methylphenidate for attention deficit hyperactivity disorder and child physical abuse: a population-based self-controlled case series study

Running title: Methylphenidate treatment and child physical abuse

Authors:

Kenneth KC Man, PhD[1,2,3*], Le Gao, MSc[1*], Wallis CY Lau, PhD[1,2,3], Min Fan, MPH[1], Prof David Coghill, MD[4,5], Esther W Chan, PhD[1,3], Celine SL Chui, PhD[3,6,7], Xue Li, PhD[1,3,8], Adrienne YL Chan, MPH[1,3,9], Prof Terry Lum, PhD[10], Hao Luo, PhD[10,11], Shiu Lun Au Yeung, PhD[7], Prof Li Wei, PhD[2,3], Kirstie HTW Wong BSc[2,12], Keith TS Tung, MPH[12], Rosa S Wong, PhD[1,12], Prof Tatia MC Lee, PhD[13,14], Prof Nirmala Rao, PhD[15], Prof Yun K Wing, MBChB[16], Patrick Ip, MPH[12**], Prof Ian CK Wong, PhD[1,2,3,17**]

(*Co-first authorship)

(**Co-senior authorship)

Author affiliations:

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[2]Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom.

[3]Laboratory of Data Discovery for Health, Hong Kong Science Park, Hong Kong Special Administrative Region, China.

[4]Department of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia.

[5]Murdoch Children's Research Institute, Melbourne, Australia.

[6]School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong,

Hong Kong Special Administrative Region, China.

[7]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[8]Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[9]Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, - Epidemiology and - Economics, University of Groningen, Groningen, The Netherlands.

[10]Department of Social Work and Social Administration, Faculty of Social Science, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[11]Department of Computer Science, The University of Hong Kong, Hong Kong

[12]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[13]State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[14]Laboratory of Neuropsychology and Human Neuroscience, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[15]Faculty of Education, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[16]Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China.

[17]Aston Pharmacy School, Aston University, Birmingham, B4 7ET, UK.

Correspondence to:

Ian CK Wong, Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, the University of Hong Kong, L2-57, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong, Tel: +852 39179441, Email: wongick@hku.hk

Patrick Ip, Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Room 115, 1/F, New Clinical Building 102 Pokfulam Road, Queen Mary Hospital, Hong Kong, Tel: +852 22554090, Email: patricip@hku.hk

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Abstract

Background: Children with attention deficit hyperactivity disorder (ADHD) are at high risk of physical abuse, related to complex etiologies including increased stress on parents and families. Hence we hypothesized that the use of methylphenidate (MPH) for ADHD would lower the risk of physical abuse in children by reducing core ADHD symptoms, negative social behavior and cognition, and indirectly lower the stress on parents. This study aimed to test this hypothesis.

Methods: A self-controlled case series study was conducted using a Hong Kong territory-wide electronic medical record database. We identified children aged 5-16 years who were treated with MPH and experienced at least one physical abuse event between 2001 and 2020. Incident physical abuse events were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes E967 and 995.54.

Results: Among 39,403 children aged 5-16 years who were started on treatment with MPH, 1,064 were included in the main analysis, of which 818 (76.9%) were male. Compared with non-medicated periods, patients experienced a higher risk of physical abuse shortly before treatment initiation (IRR, 4.49; 95% CI, 3.76-5.36), after which the risk dropped back to baseline levels during the first 90 days of treatment (IRR, 0.90; 95% CI, 0.63-1.29), followed by a further 37% reduction during subsequent treatment. A direct comparison showed that the risk decreased by 80-86% after treatment when compared to 90 days before MPH use. Similar results were found for first recurrent physical abuse events, whereas no association was identified in negative control analyses.

Conclusions: These findings are consistent with the hypothesis that controlling ADHD symptoms with MPH reduces the risk of a child becoming a victim of physical abuse.

INTRODUCTION

Physical abuse in childhood is common, with about 25% of adults reporting that they were physically abused as a child.[1,2] The consequences of child abuse include impairments to physical and mental health that can extend into adulthood, ultimately affecting economic and social development.[2] Childhood physical abuse is considered an important risk factor for depressive disorders in adulthood.[3] Previous research has shown that abuse resulted in a 2.3-fold increase in hospitalization between 2001 and 2010 in Hong Kong (HK), with recorded cases in 2010 at 7.3 per 10,000 children under 19 years.[4]

When discussing the complex etiologies of child abuse, supporting a potential victim can reduce the risk of abuse, however, it is important to acknowledge that when one individual perpetrates abuse on another, responsibility sits with the perpetrator. Children with attention deficit hyperactivity disorder (ADHD) are at higher risk than their peers of being victims of abuse, particularly physical abuse.[5-8] Multiple factors may contribute to this increased risk. As ADHD is highly heritable and has shared genes with other psychopathologies,[9,10] many parents of children with ADHD also suffer from ADHD and other psychopathologies including depression, which could potentially increase the risk for negative and suboptimal parenting practices as well as perpetrating abuse.[9] Harsh parenting is also associated with an increased interactive aggravation of ADHD and oppositional symptoms in the child. In addition, many parents find parenting a child with ADHD challenging, particularly when the ADHD is untreated.[11] Children with untreated ADHD can often push boundaries laid down by adults, and such behaviors may be viewed as disobedient and willful, further increasing parental stress and creating a cycle of escalating negative parent and child behaviors[8,12] with serious consequences including domestic violence/abuse and child abuse.[13]

Direct training and support can help parents to become more competent in dealing with ADHD children, and to adopt a more supportive, empathetic and positive parenting style. This can

improve parent-child relationships and reduces parental stress, which may lead to improved wellbeing and reduce rates of abuse for children with ADHD.[14,15]

It is however possible that reducing ADHD symptoms in the child may also be an effective approach to lowering parental stress and reducing the risk of abuse. Previous studies have suggested that medications for ADHD, such as the psychostimulant methylphenidate (MPH),[16,17] may lower the risk of physical injury.[18-20] The mechanism behind this association is likely due to a reduction of core symptoms of impulsivity, inattentiveness, and hyperactivity which results in a decreased likelihood of involvement in accidents.[18] With the well-recognized safety and acceptability profile of MPH,[21] recent meta-analyses and systematic reviews also support the efficacy of pharmacological treatments for ADHD in reducing core symptoms of the disorder.[22,23] In addition, a recent study[24] also showed that MPH treatment had a positive effect on improving parent-child interactions and social cognition such as recognition of emotions and understanding of humor among children with ADHD, through the oxytocin system. We therefore hypothesized that the use of pharmacological treatment for children and adolescents with ADHD could lower the risk of physical abuse by reducing core ADHD symptoms and improving social cognition in the child, while minimizing parental stress.[25]

In view of the global increase in ADHD medication use[16,17,26] and lack of research on the effects of ADHD medication on child physical abuse, the aim of this study was to evaluate the effect of MPH on the risk of physical abuse using advanced pharmacoepidemiological approaches[16,17] to inform evidence-based guidelines.

METHODS

Data source

This study used data from the Clinical Data Analysis and Reporting System (CDARS), the electronic health records database developed by the HK Hospital Authority (HA), a statutory body that manages all public hospitals and their ambulatory clinics in HK. The HA health services are available to all HK residents (over 7.4 million people) and cover about 80% of all hospital admissions in HK.[27] Data from CDARS have been validated and used in a variety of pharmacoepidemiological studies.[28-30] Patient-specific data in CDARS includes diagnoses, hospital admissions/discharges, and prescription/dispensing information.[31] The study protocol was approved by the institutional review board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No. UW 12-136). This is a pharmacoepidemiology study without patient contact and therefore informed consent is exempted.

Self-controlled case series design

We used a self-controlled case series (SCCS) design[32,33] to investigate the association between MPH use and child physical abuse. We have previously used SCCS to investigate the effects of MPH on various conditions,[18,28,30,34] in which patients serve as their own controls and comparisons were made within-individual who experienced both the outcome and the exposure of interest.[32] Incidence rate ratios (IRRs) were derived by comparing the rate of events during medication exposure with the rate during non-medicated periods using conditional Poisson regression. The major advantage of SCCS design over conventional study designs (e.g. cohort design) is that it implicitly controls for measured and unmeasured time-invariant confounders that vary between individuals, such as genetic factors, socioeconomic status, and underlying disease severity.[32] Furthermore, we adjusted for time-varying factors, including age, season, the Coronavirus Disease 2019 (COVID-19) stringency index in the main analysis as well as

other mental disorders and other psychotropic medications in the sensitivity analyses which potentially affect MPH prescribing.[26,35] As the COVID-19 pandemic has severely affected daily life, the COVID-19 stringency index,[36] an indicator that reflects the toughness of various regions in response to COVID-19 with a higher index representing a more stringent response measure, was further adjusted as another time-varying factor. Within-individual approaches like the SCCS design have become a common methodology in ADHD medication research over the past decade.[37] Details of the SCCS assumptions relevant to the current study are available in eAppendix 1.

Case identification

Children aged 5 to 16 years who had received at least one MPH prescription and experienced an incident physical abuse event during the study period (1 January 2001 to 31 December 2020) were identified from CDARS. The outcomes of physical abuse were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes: E967 (perpetrator of child and adult abuse, external causes of injury and poisoning) and 995.54 (child physical abuse). Child physical abuse is strictly defined as any act of commission that endangers or impairs the physical health and development of a child.[38] While under the care of HA, for every case admitted for suspected child abuse, a multi-disciplinary case conference will be held to investigate the results and evidence from different parties within the context of the child and family in order to confirm case details and plan intervention.[38] The ICD-9-CM code of physical abuse will only be inputted after the decision has been made by the conference as a statutory requirement, and therefore, the recorded diagnosis has very high validity. We included all MPH users, regardless of whether they had a record of ADHD diagnosis because MPH is almost exclusively used in children for the management of ADHD in HK. MPH is currently not licensed for narcolepsy in HK for children and the incidence of narcolepsy is between 25 and 50 per 100,000 people.[39] Hence MPH is

very unlikely to be used for narcolepsy. Furthermore, the aim of this study was to evaluate the association between MPH use and risk of physical abuse, and such definition for MPH exposure had been used in previous studies.[40,41] Atomoxetine was the only other licensed treatment for ADHD in HK and use was minimal during the study period;[26] thus observation periods were censored by atomoxetine treatment to avoid co-prescribing situations that would affect the comparisons.

We commenced follow-up at 5 years of age as MPH is not recommended for children below this age.[42] Individual observation periods began on 1 January 2001 or on the child's 5th birthday, whichever was later, and ended on 31 December 2020, on the child's 17th birthday, or the registered date of death, whichever was earlier.

Exposures and outcomes

For each study subject, all MPH prescriptions and abuse events were identified. Exposure periods were defined as the time receiving MPH, and the duration between prescription start and end dates recorded in CDARS for each prescription as a time-varying variable. More than 99% of the prescriptions recorded a start and end date. Daily dosage and the quantity prescribed were used to determine the duration of treatment if the prescription end date was not available. Median values for the exposure duration were imputed when the above information was missing. We divided the patient-time into four discrete windows: (1) 90 days before the first MPH exposure (pre-exposure period), (2) first 90 days of MPH use, (3) subsequent MPH use (> 90 days), and (4) baseline period (the patient-time that falls outside the three previously stated categories, including patient-time before pre-exposure and after completing MPH). The corresponding date of the abuse was identified as the event date. The study design and timeline for a single hypothetical participant are illustrated in Fig. 1A.

Statistical analysis

Risk of incident abuse

The association between MPH use and childhood physical abuse was calculated by comparing the rate of physical abuse during exposure periods with that during non-exposure periods. Adjusted IRRs and the corresponding 95% confidence intervals (CIs) were calculated and adjusted for by age in 1-year bands, seasonal effects and COVID-19 stringency. A 90-day pre-exposure period was added to account for the possibility that a recent physical abuse event may affect the likelihood of MPH treatment, which in turn may introduce bias into the risk estimate during treatment. We separated the first 90 days of MPH use to allow detection of any temporary changes in the risk of physical abuse; we also compared the rate of physical abuse between the pre-exposure period and MPH-exposed periods. Stratified analyses were conducted to evaluate the effects by sex.

Risk of first recurrent physical abuse

To evaluate the risk of subsequent physical abuse during MPH treatment in those who were already under vigilant surveillance after the incident physical abuse event, we further investigated the association between MPH and the risk of first recurrent physical abuse. Children with a history of physical abuse where the first recurrent physical abuse events were recorded during the individual's observational period were included. The follow-up period began on 1 January 2001, the child's 5^{th} birthday, day 7 after the incident physical abuse, or the discharge date of the incident physical abuse hospitalization episode, whichever was later, and the IRR of the subsequent physical abuse was evaluated during the different exposure windows using the same definition and analysis as outlined above (Fig. 1B).

Sensitivity and negative control analyses

Sensitivity analyses were conducted to test the validity and robustness of the initial study results: (1) different drug non-adherence scenarios, (2) redefining the start of the observation

as the latest of the first observed date of ADHD diagnosis/MPH treatment, (3) restriction to incident users of MPH, (4) >120 days of MPH exposure, (5) restricting the study period to 31 December 2019 to reduce the impact of COVID-19 on the results, (6) adding a 90-day post-exposure period, (7) adjusting for other psychiatry comorbidities, (8) adjusting for other psychiatric comorbidities and other psychotropic medication use, (9) including all types of child abuse and neglect as the outcome, (10) two negative controls using diseases of the urinary system (ICD-9-CM: 580-599) and eye infection (ICD-9-CM: 370, 373, 363.0-363.2, 372.0-372.3) as alternative outcomes, and (11) further assessment of the potential impact of any unmeasured confounders by computing the E-value.[43] Detailed descriptions of these analyses are available in eAppendix 2.

A significance level of 5% with two-side was used in all statistical analyses. R4.0.3 was used for data manipulation and analyses. We have reported the results according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. According to the formula suggested by Musonda et al.,[44] our sample size of 1,064 is able to detect an IRR of 0.826 at 5% of significance and 80% power.

RESULTS

Among 39,403 individuals aged 5 to 16 years with at least one MPH prescription, 1,064 patients had a first physical abuse event during the study period (eFig. 1 in the Supplement), of which 818 (76.9%) were male and 246 (23.1%) were female. The overall incidence of physical abuse during MPH treatment was 3.53 per 1,000 patient-years. The mean (standard deviation) age at the start of the observation was 5.53 (1.57) years, and the mean duration of follow-up per participant was 8.48 (3.29) years. The mean MPH exposure was 2.59 (2.25) years per participant. Of the 1,064 patients with physical abuse, 867 (81.5%) had a recorded ADHD diagnosis. Broader psychiatric comorbidities for these patients are reported in eTable 1 in the

Supplement. Of the 1,064 first physical abuse events, 225 occurred during the MPH treatment and 839 occurred during the non-medicated period (Table 1). The median age of the index physical abuse event was 8.6 years (IQR, 7.0-10.7 years) (eFig. 2 in the Supplement). The crude incidences of physical abuse events in different risk windows are summarized in Table 2. There were three deaths during the study period.

After adjusting for age, season and the COVID-19 stringency index, there was an increased risk of physical abuse during the 90-day period before MPH initiation (IRR, 4.49; 95% CI, 3.76-5.36). The IRR was similar to baseline levels during the first 90 days of MPH treatment (IRR, 0.90; 95% CI, 0.63-1.29) and was lower than the baseline levels during prolonged MPH treatment (IRR, 0.63; 95% CI, 0.51-0.77) (Table 2). When directly compared with the pre-exposure period (Fig. 2), the risk of physical abuse was lowered by 80% during the first 90 days of MPH treatment (IRR, 0.20; 95% CI, 0.14-0.29) and 86% in the subsequent MPH treatment period (IRR, 0.14; 95% CI, 0.11-0.18).

A similar association was observed between MPH and recurrent physical abuse. We identified 219 children who had their first recurrent physical abuse events during the observation period, with 61 events occurring during the MPH treatment period (Table 2). Compared to the non-medicated period, we found an increased risk of recurrent physical abuse during the 90-day period before MPH initiation (IRR, 1.77; 95% CI, 1.08-2.90); slightly lower risk during the first 90 days of MPH treatment (IRR, 0.41; 95% CI, 0.16-1.03); and no differences during prolonged MPH treatment (IRR, 0.78; 95% CI, 0.51-1.20) (Table 2). Comparison between the risk of recurrent physical abuse during the pre-exposure period and MPH treatment period showed an association of risk reduction of 77% (IRR, 0.23; 95% CI, 0.09-0.61) during the first 90 days of MPH treatment, and 56% (IRR, 0.44; 95% CI, 0.25-0.77) in the subsequent MPH treatment period, respectively (Fig. 2).

The sex-stratified results showed a similar pattern to the main analysis (eTable 2 in the Supplement). No association was found in all risk windows in the negative control analysis using diseases of the urinary system and eye infection as outcomes (Table 2, Fig. 2 and eTable 2). We also found a lower risk of physical abuse during the 90-day post-treatment period. After adjusting further time-varying factors, other psychiatric comorbidities and/or other psychotropic medication use, we still found a decreased risk of physical abuse after treatment initiation compared to the short period before medication use. When we analyzed all types of child abuse and neglect (n=1123) we found similar results to the main analysis of physical abuse. Other sensitivity analyses showed similar results (eFig. 3 and eTable 3 in the Supplement). The E-value analysis indicated that results were unlikely to be affected by unmeasured confounding factors (eAppendix 3 in the Supplement).

DISCUSSION

The incidence of physical abuse during the 90-day period before the start of treatment with MPH was 4.5-fold higher, returned to baseline levels in the first 90 days of MPH treatment and decreased by 37% during the subsequent treatment period when compared to the other non-medicated period. This finding suggests that the decision to start MPH treatment follows the period when the risk of physical abuse is highest compared to subsequent treatment periods, when the risk begins to fall after the initiation of MPH.

After initiation of MPH treatment, it is possible that the initial reduction in recorded child physical abuse is related to reduced contact with parents because of the disclosure or close monitoring by social care, education or healthcare professionals, rather than from the direct beneficial effects of MPH. However, we observed that the IRR of child physical abuse was lower with a longer duration of use (>90 days) i.e., beyond the initial separation period. Therefore, it is unlikely that our results are fully explained by the increased monitoring

associated with the initiation of MPH and supports the hypothesis that treating ADHD with MPH may reduce physical abuse through one of the mechanisms discussed earlier.

To further examine the sensitivity of our results to any changes in surveillance of child physical abuse, we conducted an analysis to study the risk of first recurrent physical abuse events regarding the use of MPH. The results demonstrated a similar risk to the main analysis. This subgroup analysis showed that even in a group of children who were already under close surveillance due to previous history of abuse, there was still a higher risk of physical abuse directly before MPH initiation but not in other risk periods. Such findings further support the association between MPH treatment and lower risk of physical abuse over and above the potential effects of close surveillance by professionals.

Several factors may explain why the period immediately leading up to the initiation of MPH treatment coincides with the period of higher incidence of physical abuse. The highest risk of physical abuse in children during the pre-treatment period might be a trigger for screening, diagnosis, and treatment engagement of ADHD. In clinical practice, the initiation of new medication often occurs when there are specific concerns about the child's mental and physical health. In addition, children with ADHD have a higher risk of physical abuse,[5-8] for the reasons discussed in the introduction.[45] The decision to start MPH treatment in these patients may be in response to changes in behavioral or related psychiatric problems associated with physical abuse events. In contrast, the negative control analysis using diseases of the urinary system and eye infection, which should not be associated with ADHD or MPH treatments, did not show the same risk patterns as in the primary or subgroup analyses. Furthermore, the robustness of the primary analyses was supported by the sensitivity analyses.

Previous studies have demonstrated that when children's ADHD symptoms are reduced by medication, there is an associated reduction in parental stress, less negative parenting and improved parent-child relationships.[24,46,47] We hypothesize that this could reduce the risk of

physical abuse and is supported by the study results. Another potential approach to reduce the risk of abuse for children with ADHD would be to proactively address the parental issue, for example, assisted parenting with behavioral parental training to improve the quality of parenting and reduce parental stress levels.[48-51] While we are unable to test this hypothesis with our data, all previous studies have shown that medication is the main modality of treatment for children with ADHD in Hong Kong. The availability of psychosocial interventions is inconsistent and, if available, are mostly symptom-focused with a behavioral training approach.[52-54] It is widely acknowledged that only very limited availability of evidence-based behavioral parent training programs in the publicly-funded healthcare system in HK for parents of children with ADHD. Two previous research studies have shown that parenting stress ratings remained unchanged after attending a local parental training programme "Multifamily Therapy for Children With ADHD" in HK.[53,55] After taking all the above into consideration, it is unlikely that participation in parental training programs in HK can fully explain our findings.

Despite MPH having been extensively studied using various real-world outcomes, not much was previously known about the potential effect on the risk of child physical abuse. Studies from Scandinavia and HK have reported that MPH not only improves ADHD symptoms,[22] but is also associated with lower risks of other more distal outcomes such as motor vehicle accidents,[56] traumatic brain injury,[57] substance use disorder,[58] criminality[59], and more general functional outcomes[60]. In view of all the available evidence, it is likely that the lower risk of child physical abuse observed during long-term use of MPH is partly due to the effects of medication rather than solely caused by clinical surveillance or parental training programme. A previous network meta-analysis[22] has demonstrated that MPH can reduce core symptoms in different populations. Therefore, it might be reasonable to assume that the effects of MPH on the risk of physical abuse could also be observed in other populations as well as other interventions which can control the core symptoms of a child and/or parental stress. However,

considering the different availability of pharmacological and non-pharmacological interventions in different countries or regions, further studies in different populations or interventions are highly encouraged.

Limitations

There are several limitations to our study. First, CDARS does not link data from cases seen by private medical practitioners. However, in HK, the public sector is the main provider of specialist care and there are only a few private child psychiatrists.[18,28,34] Therefore, the vast majority of patients receiving MPH should be included in this study. Another limitation is that our cohort included only clinically referred patients who had sufficiently severe ADHD symptoms and/or impairment to receive MPH treatment. Therefore, our cohort may have a higher baseline risk of physical abuse compared with non-medicated patients. However, since we applied the SCCS design, the individual baseline risk should not affect our results and conclusion. Similarly, identifying child physical abuse cases using hospital records may result in an underestimation of numbers as only severe cases would be hospitalized. Again, due to the nature of the SCCS design, this would only affect statistical power rather than the interpretation of the result. Nevertheless, our results may not be applicable to children with mild ADHD and who do not require pharmacological treatment. Additionally, as we included a comparatively long follow-up period, time-varying confounding factors might exist that could influence study results. However, in addition to the adjustment of major time-varying confounders, age and seasons, we further conducted sensitivity analyses by adjusting for various time-varying confounders including psychiatric comorbidities and medication use that did not yield any major changes in the results. Finally, the E-values in our sensitivity analysis indicated that our estimates could only be explained by such confounding effects if it was associated with both treatment and outcome by a magnitude of 9.47-13.77-times, respectively,

in addition to the confounders already addressed. Therefore, any residual confounding is unlikely to exert such powerful effects on our study conclusions.

Results from the main analysis and sensitivity analyses are consistent with our hypothesis that the use of pharmacological treatment for ADHD reduces the core ADHD symptoms and parental stress which could lead to a lower risk of physical abuse. Our study provides additional evidence to support clinical decisions regarding the prescribing of MPH to children with ADHD. Medications, together with parental behavioral training, could play an important role as part of the support package for families raising children with ADHD, creating a positive effect that lasts during long-term treatment and even beyond.

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Access to data and data analysis: KKCM and ICKW had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. KKCM and LG conducted the initial analyses, and MF did the crosscheck independently.

Data/code availability: The data that included in this study are available from the corresponding author upon reasonable request, subject to the approval of the data custodian (Hospital Authority). All relevant analysis codes are available online (https://github.com/legao513/child-abuse).

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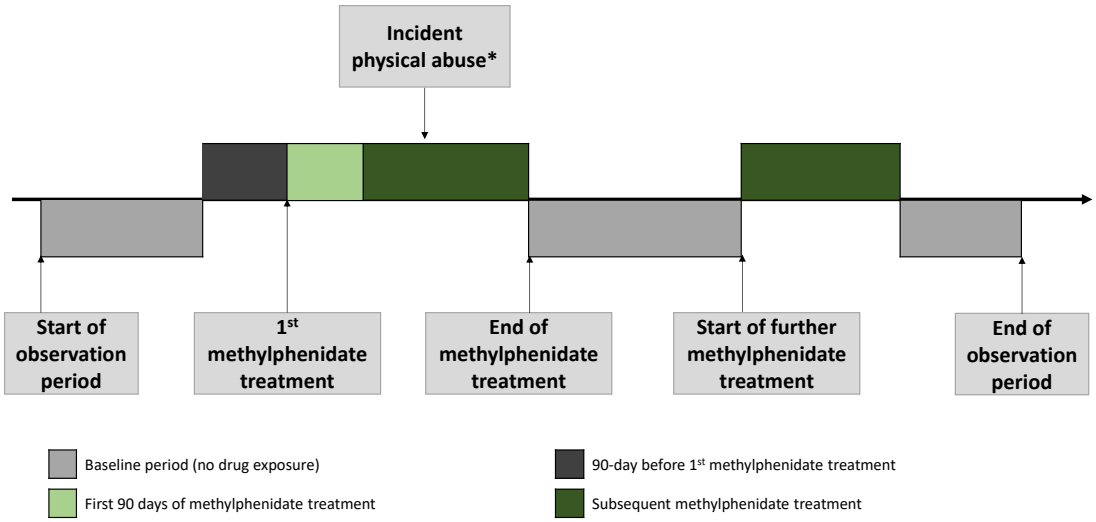
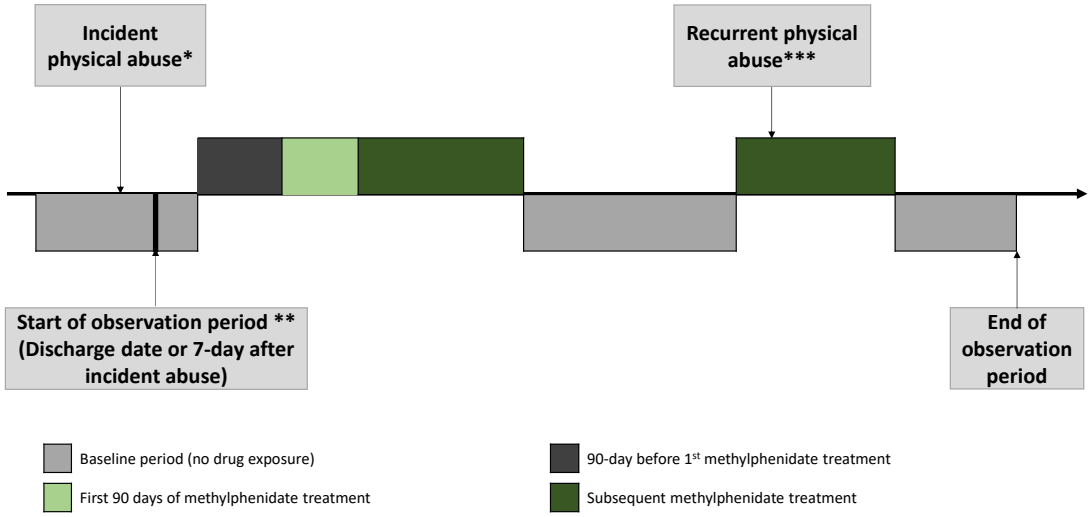


569

570 Figure 1A ***Illustration of Self-controlled Case Series Study Design (Incident physical abuse)***

571 (Note: This is a hypothetical figure for an individual. *Incident event can occur at any time

572 throughout the observation period.)



573

574 Figure 1B ***Illustration of Self-controlled Case Series Study Design (First recurrent physical abuse)***

575 (Note: This is a hypothetical figure for an individual. * Incident case can occur at any time or

576 even before the observation start date; ** New observation start date set as 1 January 2001,

on the child's 5th birthday, day 7 after the incident abuse or the discharge date of the incident abuse hospitalization episode, whichever was later; *** Recurrent case can occur at any time during the newly defined observation period.)

Risk window	Number of events	Patient-years	Crude incidence[#]	IRR* (95% CIs)	p-value
Primary analysis					
Incident physical abuse					
First 90-day of treatment	39	233.42	16.71	0.20 (0.14-0.29)	<0.001
Subsequent treatment	192	2649.36	7.25	0.14 (0.11-0.18)	<0.001
90-day before treatment	187	265.84	70.34	1.00 (-)	--
First recurrent physical abuse					
First 90-day of treatment	5	42.77	11.69	0.23 (0.09-0.61)	0.003
Subsequent treatment	63	580.42	10.85	0.44 (0.25-0.77)	0.004
90-day before treatment	22	46.89	46.92	1.00 (-)	--
Negative control analysis					
Diseases of the urinary system[a]					
First 90-day of treatment	17	105.36	16.14	1.21 (0.62-2.38)	0.57
Subsequent treatment	110	1194.4	9.21	1.02 (0.60-1.73)	0.94
90-day before treatment	17	123.34	13.78	1.00 (-)	--
Eye infection[b]					
First 90-day of treatment	25	190.27	13.14	0.89 (0.53-1.50)	0.66
Subsequent treatment	194	2193.23	8.85	0.85 (0.58-1.24)	0.40
90-day before treatment	33	224.57	14.69	1.00 (-)	--

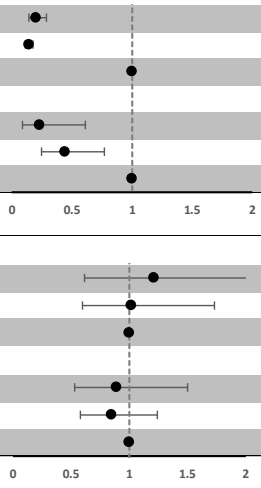


Figure 2 ***Results of direct comparison (90-day before treatment as reference group) from self-controlled case series analysis*** (Note: a, ICD-9-CM: 580-599; b, ICD-9-CM: 370, 373, 363.0-363.2, 372.0-372.3. * All estimates are adjusted for age in 1-year age-band and seasonal effect, and COVID-19 stringency index. # In 100 patient-year. Abbreviations: IRR, Incidence rate ratio, CIs, Confidence intervals)

Table 1 Patient Characteristics

	No. of Patients (%)	Mean age at baseline (years) ± SD	Median daily dosage (IQR) (mg)	Median length of prescription (IQR) (days)	Exposed period		Unexposed period	
					No. of events	Total follow-up time (patient-years)	No. of events	Total follow-up time (patient-years)
All	1064 (100)	5.53 ± 1.57	10 (10 to 20)	69 (34-111)	225	2767.98	839	6256.47
Male	818 (76.9)	5.56 ± 1.60	10 (10 to 20)	70 (39-111)	178	2162.09	640	4731.29
Female	246 (23.1)	5.44 ± 1.45	10 (10 to 20)	69 (27-111)	47	605.89	199	1525.18

Abbreviations: SD, Standard deviation; IQR, Interquartile range

590 **Table 2 Results from the self-controlled case series analysis**

Treatment	Risk window	Number of events	Patient-years	Crude incidence (In 100 patient-year)	IRR*	95% CIs		p-value
Primary analysis								
Incident physical abuse (n=1,064)								
MPH	90-day before treatment	181	252.02	71.82	4.49	3.76	5.36	<0.001
	First 90-day of treatment	34	221.16	15.37	0.90	0.63	1.29	0.57
	Subsequent treatment	191	2546.83	7.50	0.63	0.51	0.77	<0.001
	No MPH	658	6004.45	10.96	1.00	1.00	1.00	--
First recurrent physical abuse (n=219)								
MPH	90-day before treatment	22	43.27	50.84	1.77	1.08	2.90	0.02
	First 90-day of treatment	5	39.29	12.73	0.41	0.16	1.03	0.06
	Subsequent treatment	56	524.64	10.67	0.78	0.51	1.20	0.26
	No MPH	136	811.36	16.76	1.00	1.00	1.00	--
Negative control analysis								
Diseases of the urinary system (ICD-9-CM: 580-599) (n=514)								
MPH	90-day before treatment	17	123.34	13.78	1.08	0.66	1.78	0.75
	First 90-day of treatment	17	105.36	16.14	1.31	0.80	2.17	0.28
	Subsequent treatment	110	1194.38	9.21	1.10	0.84	1.46	0.48

	No MPH	370	3254.37	11.37	1.00	1.00	1.00	--
Eye infection (ICD-9-CM: 370, 373, 363.0-363.2, 372.0-372.3) (n=929)								
MPH	90-day before treatment	33	224.57	14.69	1.12	0.78	1.60	0.54
	First 90-day of treatment	25	190.27	13.14	0.99	0.66	1.50	0.98
	Subsequent treatment	194	2193.23	8.85	0.95	0.77	1.16	0.61
	No MPH	677	6147.10	11.01	1.00	1.00	1.00	--

591 Note: *All estimates are adjusted for age in 1-year age-band and seasonal effect, and COVID-19 stringency index.

592 Abbreviations: MPH, Methylphenidate, IRR, Incidence rate ratio, CIs, Confidence intervals.

Title: Methylphenidate for attention deficit hyperactivity disorder and child physical abuse: a population-based self-controlled case series study

Running title: Methylphenidate treatment and child physical abuse

Authors:

Kenneth KC Man, PhD[1,2,3*], Le Gao, MSc[1*], Wallis CY Lau, PhD[1,2,3], Min Fan, MPH[1], Prof David Coghill, MD[4,5], Esther W Chan, PhD[1,3], Celine SL Chui, PhD[3,6,7], Xue Li, PhD[1,3,8], Adrienne YL Chan, MPH[1,3,9], Prof Terry Lum, PhD[10], Hao Luo, PhD[10,11], Shiu Lun Au Yeung, PhD[7], Prof Li Wei, PhD[2,3], Kirstie HTW Wong BSc[2,12], Keith TS Tung, MPH[12], Rosa S Wong, PhD[1,12], Prof Tatia MC Lee, PhD[13,14], Prof Nirmala Rao, PhD[15], Prof Yun K Wing, MBChB[16], Patrick Ip, MPH[12**], Prof Ian CK Wong, PhD[1,2,3,17**]

(*Co-first authorship)

(**Co-senior authorship)

Author affiliations:

[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[2]Research Department of Practice and Policy, UCL School of Pharmacy, London, United Kingdom.

[3]Laboratory of Data Discovery for Health, Hong Kong Science Park, Hong Kong Special Administrative Region, China.

[4]Department of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia.

[5]Murdoch Children's Research Institute, Melbourne, Australia.

[6]School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong,

Hong Kong Special Administrative Region, China.

[7]School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[8]Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[9]Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, - Epidemiology and - Economics, University of Groningen, Groningen, The Netherlands.

[10]Department of Social Work and Social Administration, Faculty of Social Science, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[11]Department of Computer Science, The University of Hong Kong, Hong Kong

[12]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[13]State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[14]Laboratory of Neuropsychology and Human Neuroscience, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[15]Faculty of Education, The University of Hong Kong, Hong Kong Special Administrative Region, China.

[16]Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China.

[17]Aston Pharmacy School, Aston University, Birmingham, B4 7ET, UK.

Correspondence to:

Ian CK Wong, Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, the University of Hong Kong, L2-57, Laboratory Block, 21 Sassoon Road, Pokfulam, Hong Kong, Tel: +852 39179441, Email: wongick@hku.hk

Patrick Ip, Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Room 115, 1/F, New Clinical Building 102 Pokfulam Road, Queen Mary Hospital, Hong Kong, Tel: +852 22554090, Email: patricip@hku.hk

Key Words: Attention Deficit Hyperactivity Disorder, Methylphenidate, Physical Abuse, Pharmacoepidemiology, Child, Adolescent

Abstract

Background: Children with attention deficit hyperactivity disorder (ADHD) are at high risk of physical abuse, related to complex etiologies including increased stress on parents and families. Hence we hypothesized that the use of methylphenidate (MPH) for ADHD would lower the risk of physical abuse in children by reducing core ADHD symptoms, negative social behavior and cognition, and indirectly lower the stress on parents. This study aimed to test this hypothesis.

Methods: A self-controlled case series study was conducted using a Hong Kong territory-wide electronic medical record database. We identified children aged 5-16 years who were treated with MPH and experienced at least one physical abuse event between 2001 and 2020. Incident physical abuse events were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes E967 and 995.54.

Results: Among 39,403 children aged 5-16 years who were started on treatment with MPH, 1,064 were included in the main analysis, of which 818 (76.9%) were male. Compared with non-medicated periods, patients experienced a higher risk of physical abuse shortly before treatment initiation (IRR, 4.49; 95% CI, 3.76-5.36), after which the risk dropped back to baseline levels during the first 90 days of treatment (IRR, 0.90; 95% CI, 0.63-1.29), followed by a further 37% reduction during subsequent treatment. A direct comparison showed that the risk decreased by 80-86% after treatment when compared to 90 days before MPH use. Similar results were found for first recurrent physical abuse events, whereas no association was identified in negative control analyses.

Conclusions: These findings are consistent with the hypothesis that controlling ADHD symptoms with MPH reduces the risk of a child becoming a victim of physical abuse.

INTRODUCTION

Physical abuse in childhood is common, with about 25% of adults reporting that they were physically abused as a child.[1,2] The consequences of child abuse include impairments to physical and mental health that can extend into adulthood, ultimately affecting economic and social development.[2] Childhood physical abuse is considered an important risk factor for depressive disorders in adulthood.[3] Previous research has shown that abuse resulted in a 2.3-fold increase in hospitalization between 2001 and 2010 in Hong Kong (HK), with recorded cases in 2010 at 7.3 per 10,000 children under 19 years.[4]

When discussing the complex etiologies of child abuse, supporting a potential victim can reduce the risk of abuse, however, it is important to acknowledge that when one individual perpetrates abuse on another, responsibility sits with the perpetrator. Children with attention deficit hyperactivity disorder (ADHD) are at higher risk than their peers of being victims of abuse, particularly physical abuse.[5-8] Multiple factors may contribute to this increased risk. As ADHD is highly heritable and has shared genes with other psychopathologies,[9,10] many parents of children with ADHD also suffer from ADHD and other psychopathologies including depression, which could potentially increase the risk for negative and suboptimal parenting practices as well as perpetrating abuse.[9] Harsh parenting is also associated with an increased interactive aggravation of ADHD and oppositional symptoms in the child. In addition, many parents find parenting a child with ADHD challenging, particularly when the ADHD is untreated.[11] Children with untreated ADHD can often push boundaries laid down by adults, and such behaviors may be viewed as disobedient and willful, further increasing parental stress and creating a cycle of escalating negative parent and child behaviors[8,12] with serious consequences including domestic violence/abuse and child abuse.[13]

Direct training and support can help parents to become more competent in dealing with ADHD children, and to adopt a more supportive, empathetic and positive parenting style. This can

improve parent-child relationships and reduces parental stress, which may lead to improved wellbeing and reduce rates of abuse for children with ADHD.[14,15]

It is however possible that reducing ADHD symptoms in the child may also be an effective approach to lowering parental stress and reducing the risk of abuse. Previous studies have suggested that medications for ADHD, such as the psychostimulant methylphenidate (MPH),[16,17] may lower the risk of physical injury.[18-20] The mechanism behind this association is likely due to a reduction of core symptoms of impulsivity, inattentiveness, and hyperactivity which results in a decreased likelihood of involvement in accidents.[18] With the well-recognized safety and acceptability profile of MPH,[21] recent meta-analyses and systematic reviews also support the efficacy of pharmacological treatments for ADHD in reducing core symptoms of the disorder.[22,23] In addition, a recent study[24] also showed that MPH treatment had a positive effect on improving parent-child interactions and social cognition such as recognition of emotions and understanding of humor among children with ADHD, through the oxytocin system. We therefore hypothesized that the use of pharmacological treatment for children and adolescents with ADHD could lower the risk of physical abuse by reducing core ADHD symptoms and improving social cognition in the child, while minimizing parental stress.[25]

In view of the global increase in ADHD medication use[16,17,26] and lack of research on the effects of ADHD medication on child physical abuse, the aim of this study was to evaluate the effect of MPH on the risk of physical abuse using advanced pharmacoepidemiological approaches[16,17] to inform evidence-based guidelines.

METHODS

Data source

This study used data from the Clinical Data Analysis and Reporting System (CDARS), the electronic health records database developed by the HK Hospital Authority (HA), a statutory body that manages all public hospitals and their ambulatory clinics in HK. The HA health services are available to all HK residents (over 7.4 million people) and cover about 80% of all hospital admissions in HK.[27] Data from CDARS have been validated and used in a variety of pharmacoepidemiological studies.[28-30] Patient-specific data in CDARS includes diagnoses, hospital admissions/discharges, and prescription/dispensing information.[31] The study protocol was approved by the institutional review board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No. UW 12-136). This is a pharmacoepidemiology study without patient contact and therefore informed consent is exempted.

Self-controlled case series design

We used a self-controlled case series (SCCS) design[32,33] to investigate the association between MPH use and child physical abuse. We have previously used SCCS to investigate the effects of MPH on various conditions,[18,28,30,34] in which patients serve as their own controls and comparisons were made within-individual who experienced both the outcome and the exposure of interest.[32] Incidence rate ratios (IRRs) were derived by comparing the rate of events during medication exposure with the rate during non-medicated periods using conditional Poisson regression. The major advantage of SCCS design over conventional study designs (e.g. cohort design) is that it implicitly controls for measured and unmeasured time-invariant confounders that vary between individuals, such as genetic factors, socioeconomic status, and underlying disease severity.[32] Furthermore, we adjusted for time-varying factors, including age, season, the Coronavirus Disease 2019 (COVID-19) stringency index in the main analysis as well as

other mental disorders and other psychotropic medications in the sensitivity analyses which potentially affect MPH prescribing.[26,35] As the COVID-19 pandemic has severely affected daily life, the COVID-19 stringency index,[36] an indicator that reflects the toughness of various regions in response to COVID-19 with a higher index representing a more stringent response measure, was further adjusted as another time-varying factor. Within-individual approaches like the SCCS design have become a common methodology in ADHD medication research over the past decade.[37] Details of the SCCS assumptions relevant to the current study are available in eAppendix 1.

Case identification

Children aged 5 to 16 years who had received at least one MPH prescription and experienced an incident physical abuse event during the study period (1 January 2001 to 31 December 2020) were identified from CDARS. The outcomes of physical abuse were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes: E967 (perpetrator of child and adult abuse, external causes of injury and poisoning) and 995.54 (child physical abuse). Child physical abuse is strictly defined as any act of commission that endangers or impairs the physical health and development of a child.[38] While under the care of HA, for every case admitted for suspected child abuse, a multi-disciplinary case conference will be held to investigate the results and evidence from different parties within the context of the child and family in order to confirm case details and plan intervention.[38] The ICD-9-CM code of physical abuse will only be inputted after the decision has been made by the conference as a statutory requirement, and therefore, the recorded diagnosis has very high validity. We included all MPH users, regardless of whether they had a record of ADHD diagnosis because MPH is almost exclusively used in children for the management of ADHD in HK. MPH is currently not licensed for narcolepsy in HK for children and the incidence of narcolepsy is between 25 and 50 per 100,000 people.[39] Hence MPH is

very unlikely to be used for narcolepsy. Furthermore, the aim of this study was to evaluate the association between MPH use and risk of physical abuse, and such definition for MPH exposure had been used in previous studies.[40,41] Atomoxetine was the only other licensed treatment for ADHD in HK and use was minimal during the study period;[26] thus observation periods were censored by atomoxetine treatment to avoid co-prescribing situations that would affect the comparisons.

We commenced follow-up at 5 years of age as MPH is not recommended for children below this age.[42] Individual observation periods began on 1 January 2001 or on the child's 5th birthday, whichever was later, and ended on 31 December 2020, on the child's 17th birthday, or the registered date of death, whichever was earlier.

Exposures and outcomes

For each study subject, all MPH prescriptions and abuse events were identified. Exposure periods were defined as the time receiving MPH, and the duration between prescription start and end dates recorded in CDARS for each prescription as a time-varying variable. More than 99% of the prescriptions recorded a start and end date. Daily dosage and the quantity prescribed were used to determine the duration of treatment if the prescription end date was not available. Median values for the exposure duration were imputed when the above information was missing. We divided the patient-time into four discrete windows: (1) 90 days before the first MPH exposure (pre-exposure period), (2) first 90 days of MPH use, (3) subsequent MPH use (> 90 days), and (4) baseline period (the patient-time that falls outside the three previously stated categories, including patient-time before pre-exposure and after completing MPH). The corresponding date of the abuse was identified as the event date. The study design and timeline for a single hypothetical participant are illustrated in Fig. 1A.

Statistical analysis

Risk of incident abuse

The association between MPH use and childhood physical abuse was calculated by comparing the rate of physical abuse during exposure periods with that during non-exposure periods. Adjusted IRRs and the corresponding 95% confidence intervals (CIs) were calculated and adjusted for by age in 1-year bands, seasonal effects and COVID-19 stringency. A 90-day pre-exposure period was added to account for the possibility that a recent physical abuse event may affect the likelihood of MPH treatment, which in turn may introduce bias into the risk estimate during treatment. We separated the first 90 days of MPH use to allow detection of any temporary changes in the risk of physical abuse; we also compared the rate of physical abuse between the pre-exposure period and MPH-exposed periods. Stratified analyses were conducted to evaluate the effects by sex.

Risk of first recurrent physical abuse

To evaluate the risk of subsequent physical abuse during MPH treatment in those who were already under vigilant surveillance after the incident physical abuse event, we further investigated the association between MPH and the risk of first recurrent physical abuse. Children with a history of physical abuse where the first recurrent physical abuse events were recorded during the individual's observational period were included. The follow-up period began on 1 January 2001, the child's 5th birthday, day 7 after the incident physical abuse, or the discharge date of the incident physical abuse hospitalization episode, whichever was later, and the IRR of the subsequent physical abuse was evaluated during the different exposure windows using the same definition and analysis as outlined above (Fig. 1B).

Sensitivity and negative control analyses

Sensitivity analyses were conducted to test the validity and robustness of the initial study results: (1) different drug non-adherence scenarios, (2) redefining the start of the observation as the latest of the first observed date of ADHD diagnosis/MPH treatment, (3) restriction to incident users of MPH, (4) >120 days of MPH exposure, (5) restricting the study period to 31

December 2019 to reduce the impact of COVID-19 on the results, (6) adding a 90-day post-exposure period, (7) adjusting for other psychiatry comorbidities, (8) adjusting for other psychiatric comorbidities and other psychotropic medication use, (9) including all types of child abuse and neglect as the outcome, (10) two negative controls using diseases of the urinary system (ICD-9-CM: 580-599) and eye infection (ICD-9-CM: 370, 373, 363.0-363.2, 372.0-372.3) as alternative outcomes, and (11) further assessment of the potential impact of any unmeasured confounders by computing the E-value.[43] Detailed descriptions of these analyses are available in eAppendix 2.

A significance level of 5% with two-side was used in all statistical analyses. R4.0.3 was used for data manipulation and analyses. We have reported the results according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. According to the formula suggested by Musonda et al.,[44] our sample size of 1,064 is able to detect an IRR of 0.826 at 5% of significance and 80% power.

RESULTS

Among 39,403 individuals aged 5 to 16 years with at least one MPH prescription, 1,064 patients had a first physical abuse event during the study period (eFig. 1 in the Supplement), of which 818 (76.9%) were male and 246 (23.1%) were female. The overall incidence of physical abuse during MPH treatment was 3.53 per 1,000 patient-years. The mean (standard deviation) age at the start of the observation was 5.53 (1.57) years, and the mean duration of follow-up per participant was 8.48 (3.29) years. The mean MPH exposure was 2.59 (2.25) years per participant. Of the 1,064 patients with physical abuse, 867 (81.5%) had a recorded ADHD diagnosis. Broader psychiatric comorbidities for these patients are reported in eTable 1 in the Supplement. Of the 1,064 first physical abuse events, 225 occurred during the MPH treatment and 839 occurred during the non-medicated period (Table 1). The median age of the index

physical abuse event was 8.6 years (IQR, 7.0-10.7 years) (eFig. 2 in the Supplement). The crude incidences of physical abuse events in different risk windows are summarized in Table 2. There were three deaths during the study period.

After adjusting for age, season and the COVID-19 stringency index, there was an increased risk of physical abuse during the 90-day period before MPH initiation (IRR, 4.49; 95% CI, 3.76-5.36). The IRR was similar to baseline levels during the first 90 days of MPH treatment (IRR, 0.90; 95% CI, 0.63-1.29) and was lower than the baseline levels during prolonged MPH treatment (IRR, 0.63; 95% CI, 0.51-0.77) (Table 2). When directly compared with the pre-exposure period (Fig. 2), the risk of physical abuse was lowered by 80% during the first 90 days of MPH treatment (IRR, 0.20; 95% CI, 0.14-0.29) and 86% in the subsequent MPH treatment period (IRR, 0.14; 95% CI, 0.11-0.18).

A similar association was observed between MPH and recurrent physical abuse. We identified 219 children who had their first recurrent physical abuse events during the observation period, with 61 events occurring during the MPH treatment period (Table 2). Compared to the non-medicated period, we found an increased risk of recurrent physical abuse during the 90-day period before MPH initiation (IRR, 1.77; 95% CI, 1.08-2.90); slightly lower risk during the first 90 days of MPH treatment (IRR, 0.41; 95% CI, 0.16-1.03); and no differences during prolonged MPH treatment (IRR, 0.78; 95% CI, 0.51-1.20) (Table 2). Comparison between the risk of recurrent physical abuse during the pre-exposure period and MPH treatment period showed an association of risk reduction of 77% (IRR, 0.23; 95% CI, 0.09-0.61) during the first 90 days of MPH treatment, and 56% (IRR, 0.44; 95% CI, 0.25-0.77) in the subsequent MPH treatment period, respectively (Fig. 2).

The sex-stratified results showed a similar pattern to the main analysis (eTable 2 in the Supplement). No association was found in all risk windows in the negative control analysis using diseases of the urinary system and eye infection as outcomes (Table 2, Fig. 2 and eTable

2). We also found a lower risk of physical abuse during the 90-day post-treatment period. After adjusting further time-varying factors, other psychiatric comorbidities and/or other psychotropic medication use, we still found a decreased risk of physical abuse after treatment initiation compared to the short period before medication use. When we analyzed all types of child abuse and neglect (n=1123) we found similar results to the main analysis of physical abuse. Other sensitivity analyses showed similar results (eFig. 3 and eTable 3 in the Supplement). The E-value analysis indicated that results were unlikely to be affected by unmeasured confounding factors (eAppendix 3 in the Supplement).

DISCUSSION

The incidence of physical abuse during the 90-day period before the start of treatment with MPH was 4.5-fold higher, returned to baseline levels in the first 90 days of MPH treatment and decreased by 37% during the subsequent treatment period when compared to the other non-medicated period. This finding suggests that the decision to start MPH treatment follows the period when the risk of physical abuse is highest compared to subsequent treatment periods, when the risk begins to fall after the initiation of MPH.

After initiation of MPH treatment, it is possible that the initial reduction in recorded child physical abuse is related to reduced contact with parents because of the disclosure or close monitoring by social care, education or healthcare professionals, rather than from the direct beneficial effects of MPH. However, we observed that the IRR of child physical abuse was lower with a longer duration of use (>90 days) i.e., beyond the initial separation period. Therefore, it is unlikely that our results are fully explained by the increased monitoring associated with the initiation of MPH and supports the hypothesis that treating ADHD with MPH may reduce physical abuse through one of the mechanisms discussed earlier.

To further examine the sensitivity of our results to any changes in surveillance of child physical abuse, we conducted an analysis to study the risk of first recurrent physical abuse events regarding the use of MPH. The results demonstrated a similar risk to the main analysis. This subgroup analysis showed that even in a group of children who were already under close surveillance due to previous history of abuse, there was still a higher risk of physical abuse directly before MPH initiation but not in other risk periods. Such findings further support the association between MPH treatment and lower risk of physical abuse over and above the potential effects of close surveillance by professionals.

Several factors may explain why the period immediately leading up to the initiation of MPH treatment coincides with the period of higher incidence of physical abuse. The highest risk of physical abuse in children during the pre-treatment period might be a trigger for screening, diagnosis, and treatment engagement of ADHD. In clinical practice, the initiation of new medication often occurs when there are specific concerns about the child's mental and physical health. In addition, children with ADHD have a higher risk of physical abuse,[5-8] for the reasons discussed in the introduction.[45] The decision to start MPH treatment in these patients may be in response to changes in behavioral or related psychiatric problems associated with physical abuse events. In contrast, the negative control analysis using diseases of the urinary system and eye infection, which should not be associated with ADHD or MPH treatments, did not show the same risk patterns as in the primary or subgroup analyses. Furthermore, the robustness of the primary analyses was supported by the sensitivity analyses.

Previous studies have demonstrated that when children's ADHD symptoms are reduced by medication, there is an associated reduction in parental stress, less negative parenting and improved parent-child relationships.[24,46,47] We hypothesize that this could reduce the risk of physical abuse and is supported by the study results. Another potential approach to reduce the risk of abuse for children with ADHD would be to proactively address the parental issue, for

example, assisted parenting with behavioral parental training to improve the quality of parenting and reduce parental stress levels.[48-51] While we are unable to test this hypothesis with our data, all previous studies have shown that medication is the main modality of treatment for children with ADHD in Hong Kong. The availability of psychosocial interventions is inconsistent and, if available, are mostly symptom-focused with a behavioral training approach.[52-54] It is widely acknowledged that only very limited availability of evidence-based behavioral parent training programs in the publicly-funded healthcare system in HK for parents of children with ADHD. Two previous research studies have shown that parenting stress ratings remained unchanged after attending a local parental training programme "Multifamily Therapy for Children With ADHD" in HK.[53,55] After taking all the above into consideration, it is unlikely that participation in parental training programs in HK can fully explain our findings.

Despite MPH having been extensively studied using various real-world outcomes, not much was previously known about the potential effect on the risk of child physical abuse. Studies from Scandinavia and HK have reported that MPH not only improves ADHD symptoms,[22] but is also associated with lower risks of other more distal outcomes such as motor vehicle accidents,[56] traumatic brain injury,[57] substance use disorder,[58] criminality[59], and more general functional outcomes[60]. In view of all the available evidence, it is likely that the lower risk of child physical abuse observed during long-term use of MPH is partly due to the effects of medication rather than solely caused by clinical surveillance or parental training programme. A previous network meta-analysis[22] has demonstrated that MPH can reduce core symptoms in different populations. Therefore, it might be reasonable to assume that the effects of MPH on the risk of physical abuse could also be observed in other populations as well as other interventions which can control the core symptoms of a child and/or parental stress. However, considering the different availability of pharmacological and non-pharmacological

interventions in different countries or regions, further studies in different populations or interventions are highly encouraged.

Limitations

There are several limitations to our study. First, CDARS does not link data from cases seen by private medical practitioners. However, in HK, the public sector is the main provider of specialist care and there are only a few private child psychiatrists.[18,28,34] Therefore, the vast majority of patients receiving MPH should be included in this study. Another limitation is that our cohort included only clinically referred patients who had sufficiently severe ADHD symptoms and/or impairment to receive MPH treatment. Therefore, our cohort may have a higher baseline risk of physical abuse compared with non-medicated patients. However, since we applied the SCCS design, the individual baseline risk should not affect our results and conclusion. Similarly, identifying child physical abuse cases using hospital records may result in an underestimation of numbers as only severe cases would be hospitalized. Again, due to the nature of the SCCS design, this would only affect statistical power rather than the interpretation of the result. Nevertheless, our results may not be applicable to children with mild ADHD and who do not require pharmacological treatment. Additionally, as we included a comparatively long follow-up period, time-varying confounding factors might exist that could influence study results. However, in addition to the adjustment of major time-varying confounders, age and seasons, we further conducted sensitivity analyses by adjusting for various time-varying confounders including psychiatric comorbidities and medication use that did not yield any major changes in the results. Finally, the E-values in our sensitivity analysis indicated that our estimates could only be explained by such confounding effects if it was associated with both treatment and outcome by a magnitude of 9.47-13.77-times, respectively, in addition to the confounders already addressed. Therefore, any residual confounding is unlikely to exert such powerful effects on our study conclusions.

Results from the main analysis and sensitivity analyses are consistent with our hypothesis that the use of pharmacological treatment for ADHD reduces the core ADHD symptoms and parental stress which could lead to a lower risk of physical abuse. Our study provides additional evidence to support clinical decisions regarding the prescribing of MPH to children with ADHD. Medications, together with parental behavioral training, could play an important role as part of the support package for families raising children with ADHD, creating a positive effect that lasts during long-term treatment and even beyond.

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Access to data and data analysis: KKCM and ICKW had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. KKCM and LG conducted the initial analyses, and MF did the crosscheck independently.

Data/code availability: The data that included in this study are available from the corresponding author upon reasonable request, subject to the approval of the data custodian (Hospital Authority). All relevant analysis codes are available online (https://github.com/legao513/child-abuse).

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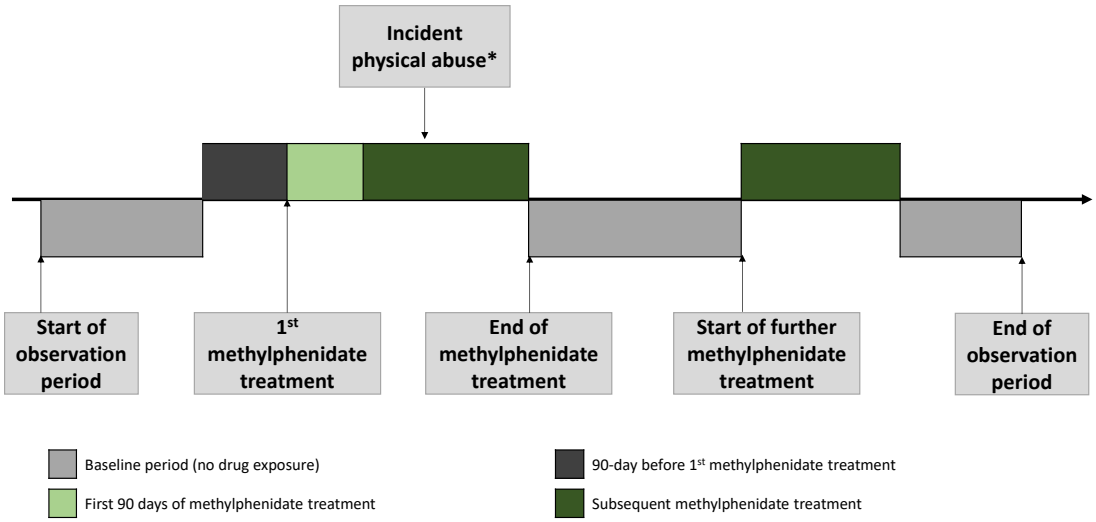


568

569 Figure 1A ***Illustration of Self-controlled Case Series Study Design (Incident physical abuse)***

570 (Note: This is a hypothetical figure for an individual. *Incident event can occur at any time

571 throughout the observation period.)

572

573 Figure 1B ***Illustration of Self-controlled Case Series Study Design (First recurrent physical abuse)***

574 (Note: This is a hypothetical figure for an individual. * Incident case can occur at any time or

575 even before the observation start date; ** New observation start date set as 1 January 2001,

on the child's 5th birthday, day 7 after the incident abuse or the discharge date of the incident abuse hospitalization episode, whichever was later; *** Recurrent case can occur at any time during the newly defined observation period.)

Risk window	Number of events	Patient-years	Crude incidence[#]	IRR* (95% CIs)	p-value
Primary analysis					
Incident physical abuse					
First 90-day of treatment	39	233.42	16.71	0.20 (0.14-0.29)	<0.001
Subsequent treatment	192	2649.36	7.25	0.14 (0.11-0.18)	<0.001
90-day before treatment	187	265.84	70.34	1.00 (-)	--
First recurrent physical abuse					
First 90-day of treatment	5	42.77	11.69	0.23 (0.09-0.61)	0.003
Subsequent treatment	63	580.42	10.85	0.44 (0.25-0.77)	0.004
90-day before treatment	22	46.89	46.92	1.00 (-)	--
Negative control analysis					
Diseases of the urinary system[a]					
First 90-day of treatment	17	105.36	16.14	1.21 (0.62-2.38)	0.57
Subsequent treatment	110	1194.4	9.21	1.02 (0.60-1.73)	0.94
90-day before treatment	17	123.34	13.78	1.00 (-)	--
Eye infection[b]					
First 90-day of treatment	25	190.27	13.14	0.89 (0.53-1.50)	0.66
Subsequent treatment	194	2193.23	8.85	0.85 (0.58-1.24)	0.40
90-day before treatment	33	224.57	14.69	1.00 (-)	--

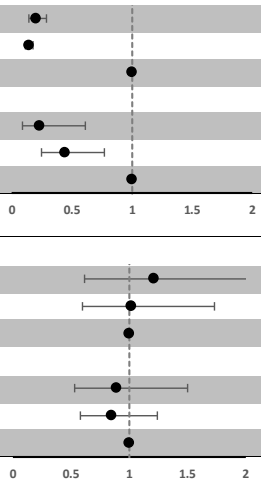


Figure 2 ***Results of direct comparison (90-day before treatment as reference group) from self-controlled case series analysis*** (Note: a, ICD-9-CM: 580-599; b, ICD-9-CM: 370, 373, 363.0-363.2, 372.0-372.3. * All estimates are adjusted for age in 1-year age-band and seasonal effect, and COVID-19 stringency index. # In 100 patient-year. Abbreviations: IRR, Incidence rate ratio, CIs, Confidence intervals)

Table 1 Patient Characteristics

	No. of Patients (%)	Mean age at baseline (years) ± SD	Median daily dosage (IQR) (mg)	Median length of prescription (IQR) (days)	Exposed period		Unexposed period	
					No. of events	Total follow-up time (patient-years)	No. of events	Total follow-up time (patient-years)
All	1064 (100)	5.53 ± 1.57	10 (10 to 20)	69 (34-111)	225	2767.98	839	6256.47
Male	818 (76.9)	5.56 ± 1.60	10 (10 to 20)	70 (39-111)	178	2162.09	640	4731.29
Female	246 (23.1)	5.44 ± 1.45	10 (10 to 20)	69 (27-111)	47	605.89	199	1525.18

Abbreviations: SD, Standard deviation; IQR, Interquartile range

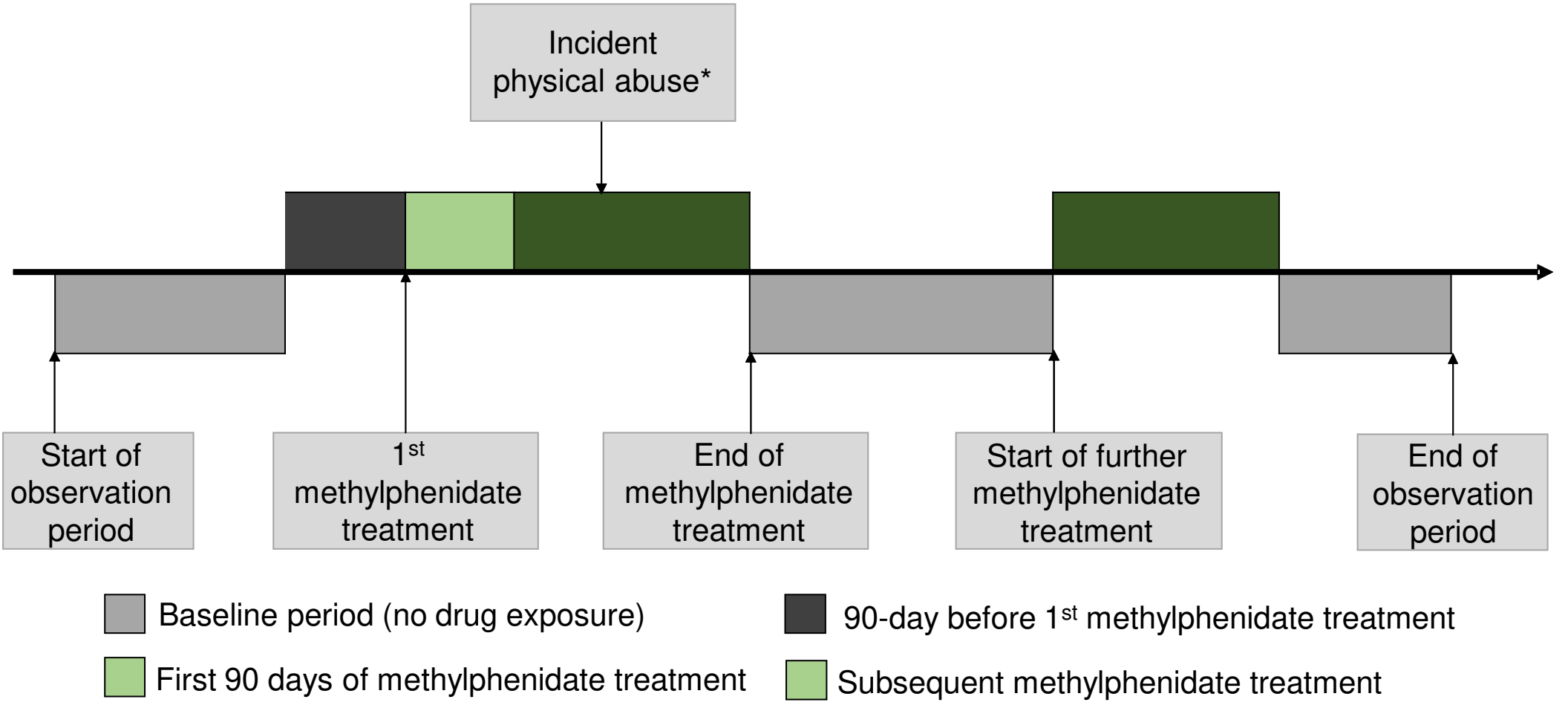
588 **Table 2 Results from the self-controlled case series analysis**

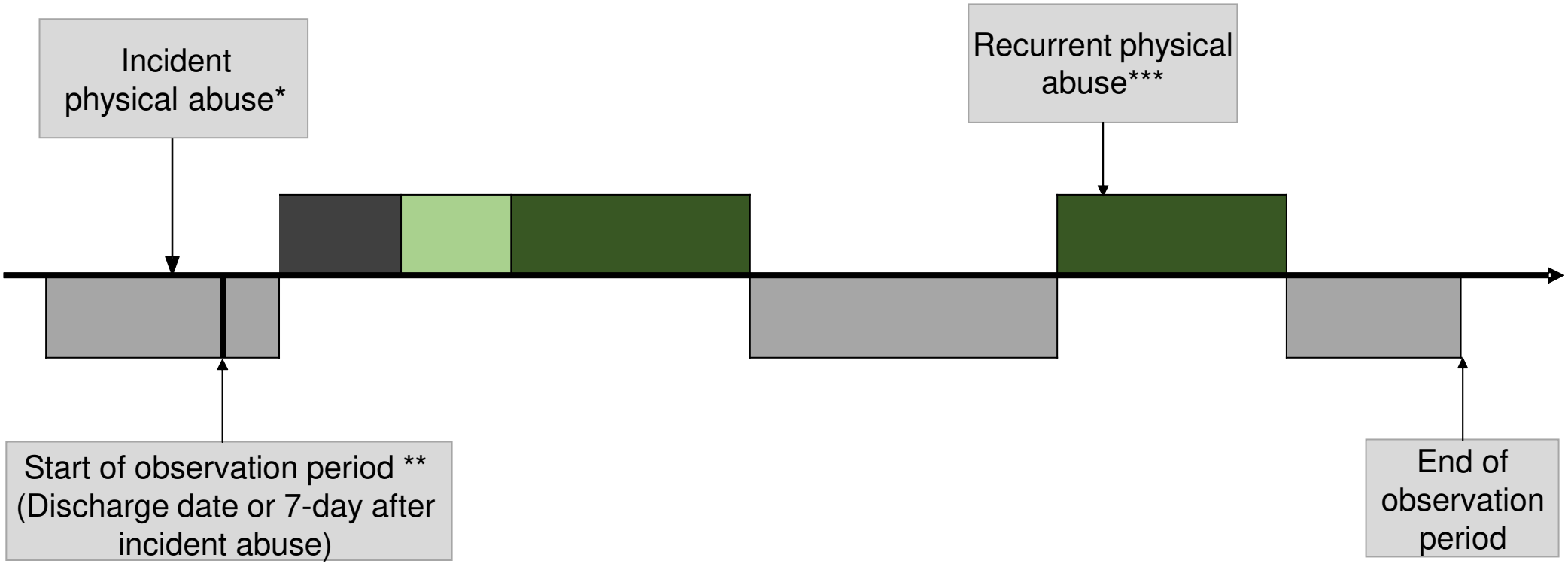
Treatment	Risk window	Number of events	Patient-years	Crude incidence (In 100 patient-year)	IRR*	95% CIs		p-value
Primary analysis								
Incident physical abuse (n=1,064)								
MPH	90-day before treatment	181	252.02	71.82	4.49	3.76	5.36	<0.001
	First 90-day of treatment	34	221.16	15.37	0.90	0.63	1.29	0.57
	Subsequent treatment	191	2546.83	7.50	0.63	0.51	0.77	<0.001
	No MPH	658	6004.45	10.96	1.00	1.00	1.00	--
First recurrent physical abuse (n=219)								
MPH	90-day before treatment	22	43.27	50.84	1.77	1.08	2.90	0.02
	First 90-day of treatment	5	39.29	12.73	0.41	0.16	1.03	0.06
	Subsequent treatment	56	524.64	10.67	0.78	0.51	1.20	0.26
	No MPH	136	811.36	16.76	1.00	1.00	1.00	--
Negative control analysis								
Diseases of the urinary system (ICD-9-CM: 580-599) (n=514)								
MPH	90-day before treatment	17	123.34	13.78	1.08	0.66	1.78	0.75
	First 90-day of treatment	17	105.36	16.14	1.31	0.80	2.17	0.28
	Subsequent treatment	110	1194.38	9.21	1.10	0.84	1.46	0.48

	No MPH	370	3254.37	11.37	1.00	1.00	1.00	--
Eye infection (ICD-9-CM: 370, 373, 363.0-363.2, 372.0-372.3) (n=929)								
MPH	90-day before treatment	33	224.57	14.69	1.12	0.78	1.60	0.54
	First 90-day of treatment	25	190.27	13.14	0.99	0.66	1.50	0.98
	Subsequent treatment	194	2193.23	8.85	0.95	0.77	1.16	0.61
	No MPH	677	6147.10	11.01	1.00	1.00	1.00	--

589 Note: *All estimates are adjusted for age in 1-year age-band and seasonal effect, and COVID-19 stringency index.

590 Abbreviations: MPH, Methylphenidate, IRR, Incidence rate ratio, CIs, Confidence intervals.


Incident physical abuse*
Start of observation period
1st methylphenidate treatment
End of methylphenidate treatment
Start of further methylphenidate treatment
End of observation period
Baseline period (no drug exposure)
90-day before 1st methylphenidate treatment
First 90 days of methylphenidate treatment
Subsequent methylphenidate treatment


Incident physical abuse*
Recurrent physical abuse***
Start of observation period ** (Discharge date or 7-day after incident abuse)
End of observation period
Baseline period (no drug exposure)
90-day before 1st methylphenidate treatment
First 90 days of methylphenidate treatment
Subsequent methylphenidate treatment

Risk window	Number of events	Patient-years	Crude incidence[#]	IRR* (95% CIs)	p-value
Primary analysis					
Incident physical abuse					
First 90-day of treatment	39	233.42	16.71	0.20 (0.14-0.29)	<0.001
Subsequent treatment	192	2649.36	7.25	0.14 (0.11-0.18)	<0.001
90-day before treatment	187	265.84	70.34	1.00 (-)	--
First recurrent physical abuse					
First 90-day of treatment	5	42.77	11.69	0.23 (0.09-0.61)	0.003
Subsequent treatment	63	580.42	10.85	0.44 (0.25-0.77)	0.004
90-day before treatment	22	46.89	46.92	1.00 (-)	--
Negative control analysis					
Diseases of the urinary system[a]					
First 90-day of treatment	17	105.36	16.14	1.21 (0.62-2.38)	0.57
Subsequent treatment	110	1194.4	9.21	1.02 (0.60-1.73)	0.94
90-day before treatment	17	123.34	13.78	1.00 (-)	--
Eye infection[b]					
First 90-day of treatment	25	190.27	13.14	0.89 (0.53-1.50)	0.66
Subsequent treatment	194	2193.23	8.85	0.85 (0.58-1.24)	0.40
90-day before treatment	33	224.57	14.69	1.00 (-)	--