Methylphenidate and the risk of burn injury among children with attention-deficit/hyperactivity disorder

Vincent Chin-Hung Chen1,2, Yao-Hsu Yang3,4, Ting Yu Kuo5, Mong-Liang Lu5,6, Wei-Ting Tseng7, Tsai-Yu Hou1, Jia-Ying Yeh7, Charles Tzu-Chi Lee8, Yi-Lung Chen9,10,∗, Min-Jing Lee1,2,∗, Michael E. Dewey11 and Michael Gossop12

1Department of Psychiatry, Chang Gung Memorial Hospital, Chiayi Branch, Chiayi, Taiwan; 2School of Medicine, Chang Gung University, Taoyuan, Taiwan; 3Health Information and Epidemiology Laboratory, Chang Gung Memorial Hospital, Chiayi, Taiwan; 4Department of Traditional Chinese Medicine, Chang Gung Memorial Hospital, Chiayi Branch, Chiayi, Taiwan; 5Department of Psychiatry & Psychiatric Research Center, Wan-Fang Hospital and Taipei Medical University, Taipei, Taiwan; 6Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; 7Department of Psychiatry, Chang Gung Memorial Hospital, Kaohsiung Branch, Chiayi, Taiwan; 8Department of Health Promotion and Health Education, National Taiwan Normal University, Taipei, Taiwan; 9Department of Healthcare Administration, Asia University, Taichung, Taiwan; 10Department of Psychology, Asia University, Taichung, Taiwan; 11Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK and 12National Addiction Centre, Institute of Psychiatry Psychology and Neuroscience, King’s College London, London, UK

Abstract

Aims. Attention-deficit/hyperactivity disorder (ADHD) is associated with a higher risk of burn injury than in the normal population. Nevertheless, the influence of methylphenidate (MPH) on the risk of burn injury remains unclear. This retrospective cohort study analysed the effect of MPH on the risk of burn injury in children with ADHD.

Method. Data were from Taiwan’s National Health Insurance Research Database (NHIRD). The sample comprised individuals younger than 18 years with a diagnosis of ADHD (n = 90 634) in Taiwan’s NHIRD between January 1996 and December 2013. We examined the cumulative effect of MPH on burn injury risk using Cox proportional hazards models. We conducted a sensitivity analysis for immortal time bias using a time-dependent Cox model and within-patient comparisons using the self-controlled case series model.

Results. Children with ADHD taking MPH had a reduced risk of burn injury, with a cumulative duration of treatment dose-related effect, compared with those not taking MPH. Compared with children with ADHD not taking MPH, the adjusted hazard ratio for burn injury was 0.70 in children taking MPH for <90 days (95% confidence interval (CI) 0.64–0.77) and 0.43 in children taking MPH for ≥90 days (95% CI 0.40–0.47), with a 50.8% preventable fraction. The negative association of MPH was replicated in age-stratified analysis using time-dependent Cox regression and self-controlled case series models.

Conclusion. This study showed that MPH treatment was associated with a lower risk of burn injury in a cumulative duration of treatment dose-related effect manner.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterised by inattention, hyperactivity, impulsivity and cognitive dysfunction (Agerbo et al., 2002). The global lifetime prevalence of ADHD is estimated to be 7.2% (Thomas et al., 2015). ADHD is significantly associated with impairments in daily life, daily functioning at school or work, and social and emotional development (Buitelaar and Medori, 2010). Furthermore, it has implications for family stress and health care resource consumption (Dittmann et al., 2014). In addition, the core symptoms of ADHD, including inattention, distractibility and impulsivity, probably account for the increased risk of unintentional injuries (Cairney, 2014). ADHD is associated with an increased risk of accident and injury (Rowe et al., 2004; Chang et al., 2014; Chang et al., 2019), leads to a shorter life expectancy, and those accidents or injuries are the most common cause of death in ADHD patients (Dalsgaard et al., 2015b; Chen et al., 2019).

Burn injuries can be a devastating event, imposing a physical, psychological and economic burden on such patients and society (Chen et al., 2014b). Children with ADHD are at an increased risk of burn injury (Mangus et al., 2004; Thomas et al., 2004; Fritz and Butz, 2007; Badger et al., 2008; Ghanizadeh, 2008). The most recent case–control study including 223 patients demonstrated that the prevalence of burn injury among children with ADHD

© The Author(s), 2020. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.
Taiwan (Lee et al., 2008). A retrospective study by Badger et al. also reported that children with ADHD or ADD were more frequently involved in activities with a high risk of burn injury and more frequently experienced mental health difficulties (Badger et al., 2008).

Pharmacotherapy is the first-line treatment for children with ADHD, and it can effectively reduce ADHD symptoms at all ages (Subcommittee on Attention-Deficit/Hyperactivity et al., 2011). Robust evidence has been reported to support methylphenidate (MPH) as preferred first-choice medications for the short-term treatment of ADHD in children and adolescents (Cortese et al., 2018). Studies have proposed that treatment with stimulants might reduce the risk of injuries in patients with ADHD (Dalsgaard et al., 2015a; Man et al., 2015; Mikolajczyk et al., 2015; Liang et al., 2017). One population-based prospective cohort study reported that treatment with ADHD drugs reduced the risk of injuries and emergency ward visits (Dalsgaard et al., 2015a). No study has evaluated whether exposure to psychostimulant treatment mitigates the risk of burn injury or examined the effect of the duration of medication administration. We therefore explored the effect of the psychostimulant MPH on the risk of burn injury in patients with ADHD and whether the mitigating effects are related to the duration of exposure, by using a nationwide population-based dataset in Taiwan. We hypothesised that ADHD medication was linked to a lower risk of burn injury.

Materials and methods

Study design and participants

In this retrospective cohort study, we used data from the Taiwan National Health Insurance Research Database (NHIRD) under the aegis of the National Health Research Institute, which includes data on outpatient, ambulatory and hospital inpatient care, as well as on dental services. Taiwan launched a single-payer National Health Insurance programme on 1 March 1995, covering the delivery of all health care services to 99.5% of the national population (Ng, 1997). The NHIRD holds some important information, such as patients’ demographic data, the medical institution visited, diagnostic codes, the drugs prescribed, the date of any prescriptions given and any claimed medical expenses. The database has been used in many epidemiologic studies in Taiwan (Lee et al., 2017; Chen et al., 2018). Several validation studies have shown that the data set represents modest to high validity and positive predictive values (Hsieh et al., 2019).

The ADHD cohort was selected from NHIRD. It included individuals younger than 18 years by 31 December 2013. For ensuring the diagnosis of ADHD, we only recruited participants with ADHD who received at least one inpatient diagnosis of ADHD (International Classification of Disease, 9th revision [ICD-9] code: 314) or more than two outpatient diagnoses within 1 year between 1 January 1996 and 31 December 2011.

Outcomes

The main outcome of this study was burn injury (ICD-9-CM codes: 940–949). Patients with a diagnosis of burn injury (Mangus et al., 2004) before the diagnosis of ADHD were excluded. Patients with ADHD were followed up for the incidence of burn injury as an outcome, or until age 18, or to the end of 2013.

Assessment of other characteristics

Several covariates were selected, including sex, age, urbanisation level of residence and seizure (ICD-9 code: 345). Psychiatric comorbidity included intellectual disability (ICD-9 codes: 317–319), autism (ICD-9 code: 299), conduct disorder (ICD-9 code: 312), opposition defiant disorder (ICD-9-CM code: 313.81), anxiety (ICD-9 code: 300) and depression (ICD-9 codes: 296.2, 296.3, 300.4 and 311). Baseline medication use was identified based on a prescription of any benzodiazepine (ATC codes: N03AE, N05BA and N05CD), benzodiazepine-related drugs (ATC code: N05CF), antipsychotic (ATC code: N05A) or antidepressant (ATC code: N06A) 12 months prior to the burn injury diagnosis.

MPH (ATC code: N06BA04) has been the only stimulant approved for treating ADHD in Taiwan and is regarded as the first-line treatment for ADHD according to Taiwan’s National Insurance. In 2017, atomoxetine (ATX), a non-stimulant, was also approved for ADHD treatment in Taiwan. However, compared with MPH, ATX has a much lower prescription rate (4% in all patients with ADHD) (Lee et al., 2016). ATX is recommended only for cases where patients have insufficient treatment outcomes (i.e. inefficacy and intolerability) from MPH. Thus, it can be reasonably assumed that patients who received ATX have had prior MPH treatment exposure. Therefore, we included patients with only MPH exposure in this study. We investigated the treatment duration effect by examining MPH use in the ADHD cohort. The definition of treatment duration was the cumulative length of MPH exposure (days) within the follow-up period until end-points of burn injury, death or the end of the study. The ADHD population was divided into three subgroups based on the duration of MPH prescription: 0, <90 and ≥90 days. This study was reviewed and approved by the Institutional Review Board of Chang Gung Memorial Hospital.

Statistical analysis

All data management and statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). To describe the distribution of the study population, a χ² test was used to compare the characteristics between the ADHD and control groups. The adjusted risk of burn injury between ADHD with and without MPH medication and the preventable fraction of MPH medication among individuals with ADHD was estimated using a Cox proportional hazards regression model. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). We calculated the duration of medication use for each patient with ADHD and tested the cumulative effect on the burn incidence according to stratification into three groups, 0, <90, ≥90 days, by adjusting for covariates in competing risk-adjusted Cox regression models (Allgulander and Fisher, 1986). Age-stratified analysis was also conducted to examine the cumulative effect of MPH at three different age groups: (1) age <6, (2) age between 6 and 12, and (3) age ≥12 and <18. Participants’ age is calculated by the difference between their birthdate and the end of follow-up (i.e. 31 December 2013) (Allgulander and Fisher, 1986). To examine the immortal time bias, a sensitivity analysis using time-dependent Cox hazards regression analysis was performed. We also estimated the preventable fraction: the proportion of incidents of burn in patients with ADHD not taking MPH that could be prevented by MPH medication.
For within-patient comparisons, we used the self-controlled case series (SCCS) model, in which time was divided into periods similar to the stratified Cox regression model, with each patient as a separate stratum (i.e. the patient served as his or her own control). The risk estimated from the SCCS model indicates the risk of burn injury when individuals took MPH compared to the period when they did not take MPH. The SCCS model automatically adjusts for all time-invariant factors (e.g. sex) for the same patient before and during the follow-up. The effect period for MPH was set at 1–3 months based on previous studies (Chen et al., 2014a; Chang et al., 2016). Thus, the effect period was split into three 1-month effect periods: 0–30, 31–60 and 61–90 days from the end of each treatment period. Finally, we combined the three effect periods into one to report the average pooled estimate of MPH use for burn injury. Figure 1 is present to illustrate the SCCS study design in this cohort. The SCCS model was applied using the SCCS package in R (Farrington et al., 2018). Furthermore, a moderation analysis based on the SCCS model was conducted to examine whether the neurodevelopmental disorders (i.e. intellectual disability and autistic spectrum disorder) modify the effect of MPH on burn injury in children and adolescents with ADHD.

Results

Table 1 shows the characteristics of children with ADHD stratified to three subgroups: 0 days (22 347 patients), <90 days (17 766 patients) and ≥90 days (50 521 patients). The risk of burn injury was 6.7, 4.5 and 2.9% in the three groups, respectively (p < 0.0001). The preventable fraction of MPH medication was 0.508, indicating that 50.8% (11 352 patients) incidence of burn injury could be prevented if they took MPH medication.

Table 2 shows the influences of the MPH cumulative effect on the burn risk among patients with ADHD and different age groups. For the whole sample, compared with patients with ADHD not taking MPH, those taking MPH for <90 days had an adjusted HR of 0.70 for burn injury (CI 0.64–0.77) and those taking MPH for ≥90 days had an adjusted HR of 0.43 (95% CI 0.40–0.47). The results of the trend test were significant (p < 0.01). In addition, age-stratified analyses revealed a similar pattern in different age groups and the adjusted HR ranged from 0.55 to 0.87 for those taking MPH for <90 days and 0.32 to 0.55 for those taking MPH for ≥90 days, respectively. Table 3 shows the sensitivity analysis which confirmed the inverse association between MPH and risk of burn injury using the time-dependent model.

Table 4 presents the effect of MPH on burn injury within patients with ADHD, which was determined using the SCCS model. Within-patient comparisons revealed a significant reduction in the risk of burn injury in effect periods from 0 to 30 (HR 0.49, 95% CI 0.44–0.55), 30 to 60 (HR 0.46, 95% CI 0.40–0.54) and 60 to 90 days (HR 0.51, 95% CI 0.42–0.41). An average pooled estimate of these effect periods indicated an HR of 0.49 and 95% CI of 0.45–0.53. Furthermore, we found that the effect of MPH on burn injury was attenuated in participants with ADHD and intellectual disability (p = 0.002), but not in autistic spectrum disorder (p > 0.05). The protective effect (RR) was decreased from 0.49 in participants with ADHD to 0.61 in participants with ADHD and intellectual disability.

Discussion

To our knowledge, this is the first nationwide population-based cohort study to investigate the effect of medication usage on the risk of burn injury in ADHD patients. Our study looked into the risk of burn injury specifically and added to the existing evidence that MPH treatment was associated with a lower risk of burn injury among ADHD children. We found a lower incidence of burn injury in patients with ADHD prescribed MPH in the whole sample and different age subgroups. In total, 50.8% incidence of burn injury among patients with ADHD not taking MPH could be prevented if they took MPH medication.

Research has indicated that ADHD patients have a higher risk for burn injury than non-ADHD controls (Fredriksen et al., 2014). The potential explanations include impulsivity, attention-deficit-related carelessness, overlooking danger, impairment in executive function and motor coordination. This study found
that ADHD patients prescribed MPH had a reduced likelihood of burn injury and prior studies have also demonstrated correlations between burn injury and MPH. One retrospective chart review examined children admitted to a burn care facility with respect to ADHD diagnosis or history of stimulant prescription and found that although a high percentage of these children (nearly 89%) had been prescribed stimulant medication, approximately 42% of them had not taken their usual dose of MPH on the day of the burn injury; they were injured by impulsive fire-play behaviour (Thomas et al., 2004). In the present study, an average within-patient risk reduction of 51% was noted from comparing periods of time exposed to stimulant medication and unexposed periods. We expand on prior findings that MPH treatment plays a role in the reduced risk of burn injury in patients with ADHD. Several studies have suggested benefits on core symptoms and cognitive performance improvement after stimulant treatment (Fredriksen et al., 2014; Setyawan et al., 2015).

We also investigated the cumulative effect of MPH (using the cumulative duration of MPH prescription) on the risk of burn injury in patients with ADHD and found that the burn injury risk reduction was linked to an increased MPH usage duration. Studies have identified attenuation in the risk of fracture, suicide and traumatic brain injury to be associated with the dosage effect of MPH treatment (Chen et al., 2017; Liang et al., 2017; Liao et al., 2018). Long-term stimulant treatment normalises delayed brain development and yield to neuroadaptive and neurochemical change (Schweren et al., 2013). Functional magnetic resonance imaging studies have also shown that exposure to psychostimulants may alter brain function connectivity and activity (van der Marel et al., 2015). Our findings extend previous evidence and hold implications for clinical practice – sufficient duration of MPH treatment may be protective against burn injury.

This nationwide population-based study has several strengths. First, the nationally representative sample was substantial and minimised selection bias. Second, patients with ADHD were identified through physician-based diagnoses. Third, all MPH prescriptions are recorded in the NHIRD, avoiding misclassification.

### Table 1. Characteristics of children with ADHD with and without MPH use

| Variables                                             | Frequency | MPH = 0 day | 0–90 days | ≥90 days | p value |
|-------------------------------------------------------|-----------|-------------|-----------|----------|---------|
|                                                       | N         | %           | N         | %        | N       | %       | p value |
| Total                                                 | 90,634    | 22,347      | 17,766    | 50,521   |         |         |         |
| Gender                                                |           |             |           |          | <0.0001 |
| Female                                                | 18,512    | 20.4        | 5,550     | 24.8     | 3,863   | 21.7    | 9,099   | 18.0    |<0.0001 |
| Male                                                  | 72,122    | 9.6         | 16,797    | 75.2     | 13,903  | 78.3    | 41,422  | 82.0    |         |
| Age                                                   |           |             |           |          | <0.0001 |
| 0–5                                                   | 20,372    | 22.5        | 9,157     | 41.0     | 3,016   | 17.0    | 8,199   | 16.2    |<0.0001 |
| 6–11                                                  | 62,880    | 69.4        | 11,951    | 53.5     | 12,738  | 71.7    | 38,191  | 75.6    |         |
| 12–18                                                 | 7,382     | 8.1         | 1,239     | 5.5      | 2,012   | 11.3    | 4,131   | 8.2     |         |
| Covariates                                            |           |             |           |          | <0.0001 |
| Seizure                                               | 4,067     | 4.5         | 1,175     | 5.3      | 732     | 4.1     | 2,160   | 4.3     |<0.0001 |
| Intellectual disability                               | 431       | 0.5         | 161       | 0.7      | 83      | 0.5     | 187     | 0.4     |<0.0001 |
| Autism                                                | 8,603     | 9.5         | 3,042     | 13.6     | 1,523   | 8.6     | 4,038   | 8.0     |<0.0001 |
| Conduct disorder                                      | 3,452     | 3.8         | 724       | 3.2      | 641     | 3.6     | 2,087   | 4.1     |<0.0001 |
| Opposition defiant disorder                           | 5,132     | 5.7         | 280       | 1.3      | 725     | 4.1     | 4,127   | 8.2     |<0.0001 |
| Anxiety                                               | 18,528    | 20.4        | 2,115     | 9.5      | 3,025   | 17.0    | 13,388  | 26.5    |<0.0001 |
| Depression                                            | 2,368     | 2.6         | 373       | 1.7      | 459     | 2.6     | 1,536   | 3.0     |<0.0001 |
| Benzodiazepines use                                   | 3,045     | 3.4         | 673       | 3.0      | 615     | 3.5     | 1,757   | 3.5     |0.0039  |
| Z-drugs use                                           | 165       | 0.2         | 22        | 0.1      | 30      | 0.2     | 113     | 0.2     |0.0011  |
| Antipsychotics use                                    | 5,340     | 5.9         | 849       | 3.8      | 828     | 4.7     | 3,663   | 7.3     |<0.0001 |
| Antidepressants use                                   | 2,765     | 3.1         | 405       | 1.8      | 456     | 2.6     | 1,904   | 3.8     |<0.0001 |
| Urbanised level of residence                          |           |             |           |          | <0.0001 |
| 1 (City)                                              | 32,557    | 35.9        | 9,058     | 40.5     | 5,962   | 33.6    | 17,537  | 34.7    |<0.0001 |
| 2                                                     | 43,111    | 47.6        | 10,142    | 45.4     | 8,685   | 48.9    | 24,284  | 48.1    |         |
| 3                                                     | 10,246    | 11.3        | 2,203     | 9.9      | 2,189   | 12.3    | 5,854   | 11.6    |         |
| 4 (Villages)                                          | 4,720     | 5.2         | 944       | 4.2      | 930     | 5.2     | 2,846   | 5.6     |         |
| Burn injury                                           | 3,742     | 4.1         | 1,494     | 6.7      | 792     | 4.5     | 1,456   | 2.9     |<0.0001 |

https://doi.org/10.1017/S2045796020000608 Published online by Cambridge University Press
bias. Also, by excluding burn injuries prior to ADHD diagnosis, the reverse causal relationship between ADHD and burn injury was eliminated. Finally, we used different models to demonstrate the robust treatment effect of MPH on burn injury. The between-subject treatment effect was observed in the Cox proportional hazards models. We found a significant cumulative duration of treatment dose-related effect of MPH treatment on burn risk, whereas within-subject treatment effects were assessed using the SCCS model. Some studies have also used the within-subject methodology (i.e. SCCS or case-crossover study design) to examine the effect of MPH on unintentional injuries (Ruiz-Goikoetxea et al., 2018); however, these studies suffered from the small sample size because their sample size merely ranged from 328 to 4934 (Ruiz-Goikoetxea et al., 2018). As a result, they focused on any type of injury, and they were not able to examine some specific causes of injury. For example, in Raman et al.’s study, they had 328 individuals with ADHD who experienced an incident medically attended injury event and received at least one prescription for stimulant medication, but only 1.2% (4/328) reported experiencing burn injury (Raman et al., 2013). In our study, because of the enforcement rules of the National Health Insurance in Taiwan, citizens in Taiwan are required to enrol in this insurance programme, resulting in sufficient data for examining this issue.

### Table 2. Cox proportional hazards model for burn injury in children with ADHD and age-stratified analysis

| Methylphenidate use | Unadjusted analysis | Adjusted analysis modela |
|---------------------|---------------------|-------------------------|
|                     | HR  | 95% CI  | p value | HR  | 95% CI  | p value |
| Whole sample        |     |         |         |     |         |         |
| 0 day (ref.)        | 1.00| –       | –       | 1.00| –       | –       |
| <90 days            | 0.65| 0.60–0.71| <0.0001| 0.70| 0.64–0.77| <0.0001|
| ≥90 days            | 0.39| 0.37–0.42| <0.0001| 0.43| 0.40–0.47| <0.0001|
| Age < 6             |     |         |         |     |         |         |
| 0 day (ref.)        | 1.00| –       | –       | 1.00| –       | –       |
| <90 days            | 0.54| 0.46–0.63| <0.0001| 0.55| 0.46–0.64| <0.0001|
| ≥90 days            | 0.31| 0.27–0.35| <0.0001| 0.32| 0.28–0.37| <0.0001|
| 6 ≤ age < 12        |     |         |         |     |         |         |
| 0 day (ref.)        | 1.00| –       | –       | 1.00| –       | –       |
| <90 days            | 0.88| 0.78–0.99| 0.0278 | 0.87| 0.78–0.98| 0.0213 |
| ≥90 days            | 0.53| 0.48–0.59| <0.0001| 0.54| 0.48–0.60| <0.0001|
| 12 ≤ age < 18       |     |         |         |     |         |         |
| 0 day (ref.)        | 1.00| –       | –       | 1.00| –       | –       |
| <90 days            | 0.83| 0.54–1.28| 0.3983 | 0.84| 0.55–1.31| 0.4443 |
| ≥90 days            | 0.55| 0.37–0.82| 0.0038 | 0.55| 0.37–0.83| 0.0045 |

*aAdjusted by seizure, intellectual disability, autism, conduct disorder, oppositional defiant disorder, anxiety, depression and psychotropic use (benzodiazepine, Z-drugs, antipsychotics and antidepressants).

### Table 3. Time-dependent Cox proportional hazards model for burn injury in children with ADHD

| Variables  | Unadjusted analysis | Adjusted analysis modela |
|------------|---------------------|-------------------------|
|            | HR  | 95% CI  | p value | HR  | 95% CI  | p value |
| Methylphenidate |     |         |         |     |         |         |
| 0 DDD (ref.) | 1.00| –       | –       | 1.00| –       | –       |
| >0 day      | 0.65| 0.61–0.70| <0.0001| 0.72| 0.67–0.78| <0.0001|

*aAdjusted by seizure, intellectual disability, autism, conduct disorder, oppositional defiant disorder, anxiety, depression and psychotropic use (benzodiazepine, Z-drugs, antipsychotics and antidepressants).*
This study had several limitations. First, the accuracy of disease diagnoses for ADHD or burn injury has not been documented. Second, information on drug adherence was lacking. Third, we did not evaluate the therapeutic effect of non-pharmacological treatment because behavioral therapy and psychosocial support were not fully registered in the NHIRD. Finally, the lack of MPH use in some patients may be due to a worsening of symptoms, and we did not have information on the severity of ADHD.

In conclusion, MPH treatment was linked to a lower risk of burn injury in children with ADHD, and the effect was stronger with longer MPH follow-up.

Data. These data were owned by the National Health Research Institutes. The present study was based on the National Health Insurance Research Database provided by the Central Bureau of National Health Insurance, the Department of Health, and managed by the National Health Research Institutes.

Acknowledgements. The authors would like to thank the staff of the Health Information and Epidemiology Laboratory for their comments and assistance in the data analysis.

Financial Support. This work was supported by grants from the Chang Gung Memorial Hospital ( CLRPG6G0042, CLRPG6G0043).

Conflict of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

References

Agero E, Nordentoft M and Mortensen PB (2002) Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. BMJ (Clinical Research Ed.) 325, 74.

Allgulander C and Fisher LD (1986) Survival analysis (or time to an event analysis), and the Cox regression model – methods for longitudinal psychiatric research. Acta Psychiatrica Scandinavica 74, 529–535.

Badger K, Anderson L and Kagan RJ (2008) Attention deficit-hyperactivity disorder in children with burn injuries. Journal of Burn Care and Research 29, 724–729.

Buitemaar J and Medori R (2010) Treating attention-deficit/hyperactivity disorder beyond symptom control alone in children and adolescents: a review of the potential benefits of long-acting stimulants. European Child and Adolescent Psychiatry 19, 325–340.

Cairney J (2014) Deficits in attention, motor control, and perception and increased risk of injury in children. Developmental Medicine and Child Neurology 56, 1040–1041.

Chang Z, Lichtenstein P, D’Onofrio BM, Sjolander A and Larsson H (2014) Serious transport accidents in adults with attention-deficit/hyperactivity disorder and the effect of medication: a population-based study. JAMA Psychiatry 71, 319–325.

Chang Z, D’Onofrio BM, Quinn PD, Lichtenstein P and Larsson H (2016) Medication for attention-deficit/hyperactivity disorder and risk: a nationwide longitudinal cohort study. Biological Psychiatry 80, 916–922.

Chang Z, Ghiardi L, Quinn PD, Asherson P, D’Onofrio BM and Larsson H (2019) Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. Biological Psychiatry 86, 335–343.

Chen Q, Sjolander A, Runeson B, D’Onofrio BM, Lichtenstein P and Larsson H (2014a) Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. BMJ (Clinical Research Ed.) 348, g3769.

Chen SH, Chen YC, Chen TJ and Ma H (2014b) Epidemiology of burns in Taiwan: a nationwide report including inpatients and outpatients. Burns: Journal of the International Society for Burn Injuries 40, 1397–1405.

Chen VC, Yang YH, Liao YT, Kuo TY, Liang HY, Huang KY, Huang YC, Lee Y, McIntyre RS and Lin TC (2017) The association between methylphenidate treatment and the risk for fracture among young ADHD patients: a nationwide population-based study in Taiwan. PLoS ONE 12, e0173762.

Chen VC, Wu SI, Huang KY, Yang YH, Kuo TY, Liang HY, Huang KL and Gossop M (2018) Herpes zoster and dementia: a nationwide population-based cohort study. Journal of Clinical Psychiatry 79, 16m11312.

Chen VC, Chan HL, Wu SI, Lee M, Lu ML, Liang HY, Dewey ME, Stewart R and Lee CT (2019) Attention-deficit/hyperactivity disorder and mortality: a nationwide study in Taiwan. JAMA Network Open 2, e198714.

Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, Atkinson LZ, Tessari L, Banaschewski T, Coghill D, Hollis C, Simonoff E, Zuddas A, Barbui C, Purgato M, Steinhausen H-C, Shokraneh F, Xia J and Cipriani A (2018) Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. The Lancet Psychiatry 5, 727–738.

Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS and Simonsen M (2015a) Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. The Lancet Psychiatry 2, 702–709.

Dalsgaard S, Ostergaard SD, Leckman JF, Mortensen PB and Pedersen MG (2015b) Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet (London, England) 385, 2190–2196.

Dittmann RW, Banaschewski T, Schacht A and Wehmeier PM (2014) Findings from the observational COMPLY study in children and adolescents with ADHD: core symptoms, ADHD-related difficulties, and patients’ emotional expression during psychostimulation or nonstimulant ADHD treatment. Attention Deficit and Hyperactivity Disorders 6, 291–302.

Farrington P, Whitaker H and Weldelessaie YG (2018) Self-Controlled Case Series Studies: A Modelling Guide with R. San Francisco, CA: Chapman and Hall/CRC.

Fredriksen M, Dahl AA, Martinsen EW, K lungsøy O, Haavik J and Peleikis JAMA (2014) Survival analysis (or time to an event analysis), and the Cox regression model – methods for longitudinal psychiatric research. Acta Psychiatrica Scandinavica 74, 529–535.

Gossop M, Haavik J and Peleikis JAMA (2014) Survival analysis (or time to an event analysis), and the Cox regression model – methods for longitudinal psychiatric research. Acta Psychiatrica Scandinavica 74, 529–535.

Hartvigsen J, Hancock BD, Stening F, Hemming A, McElduff P, Haarbo J, Bovbjerg BE, Bundgaard M, Leffers H, Edstedt-Granstrom A, Pedersen IB and Vestergaard M (2013) The epidemiology of attention-deficit/hyperactivity disorder in adults: a systematic review and network meta-analysis. JAMA Internal Medicine 173, 1713–1727.

Fritz KM and Butz C (2007) Attention deficit/hyperactivity disorder and pediatric burn injury: important considerations regarding premorbid risk. Current Opinion in Pediatrics 19, 565–569.

Ghanizadeh A (2008) Small burns among out-patient children and adolescents with attention deficit hyperactivity disorder. Burns: Journal of the International Society for Burn Injuries 34, 546–548.

Hsieh CY, Su CC, Shao SC, Sung SF, Lin SJ, Kao Yang YH and Lai EC (2019) Taiwan’s National Health Insurance Research Database: past and future. Clinical Epidemiology 11, 349–358.

Lee MJ, Yang KC, Shyu YC, Yuan SS, Yang CJ, Lee SY, Lee TL and Wang LJ (2016) Attention-deficit hyperactivity disorder, its treatment with...
medication and the probability of developing a depressive disorder: a nationwide population-based study in Taiwan. *Journal of Affective Disorders* **189**, 110–117.

Lee MJ, Lee SY, Yuan SS, Yang CJ, Yang KC, Lee TL, Sun CC, Shyu YC and Wang LJ (2017) Comorbidity of narcolepsy and depressive disorders: a nationwide population-based study in Taiwan. *Sleep Medicine* **39**, 95–100.

Liang SH, Yang YH, Kuo TY, Liao YT, Lin TC, Lee Y, McIntyre RS, Kelsen BA, Wang TN and Chen VC (2018) Dosage of methylphenidate and traumatic brain injury in ADHD: a population-based study in Taiwan. *European Child and Adolescent Psychiatry* **27**, 279–288.

Mangus RS, Bergman D, Zieger M and Coleman JJ (2004) Burn injuries in children with attention-deficit/hyperactivity disorder. *Burns: Journal of the International Society for Burn Injuries* **30**, 148–150.

Man KK, Chan EW, Coghill D, Douglas I, Ip P, Leung LP, Tsui MS, Wong WH and Wong IC (2015) Methylphenidate and the risk of trauma. *Pediatrics* **135**, 40–48.

Ng CH (1997) The stigma of mental illness in Asian cultures. *Australian and New Zealand Journal of Psychiatry* **31**, 382–390.

Raman SR, Marshall SW, Haynes K, Gasney BN, Naftel AJ and Stürmer T (2013) Stimulant treatment and injury among children with attention-deficit hyperactivity disorder: an application of the self-controlled case series study design. *Injury Prevention* **19**, 164–170.

Rowe R, Maughan B and Goodman R (2004) Childhood psychiatric disorder and unintentional injury: findings from a national cohort study. *Journal of Pediatric Psychology* **29**, 119–130.

Ruiz-Goioketxea M, Cortese S, Aznarez-Sanado M, Magallon S, Alvarez Zallo N, Luis EO, de Castro-Manglano P, Soutullo C and Arrondo G (2018) Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: a systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews* **84**, 63–71.

Schweren LJ, de Zeeuw P and Durston S (2013) MR imaging of the effects of methylphenidate on brain structure and function in attention-deficit/hyperactivity disorder. *European Neuropsychopharmacology* **23**, 1151–1164.

Sethyawan J, Fridman M, Hodgkins P, Quintero J, Erdem BH, Katic BJ and Harpin V (2015) Relationship between symptom impairment and treatment outcome in children and adolescents with attention-deficit/hyperactivity disorder: a physician perspective. *Attention Deficit and Hyperactivity Disorders* **7**, 75–87.

Thomas CR, Ayoub M, Rosenberg R, Robert RS and Meyer WJ (2004) Attention deficit hyperactivity disorder & pediatric burn injury: a preliminary retrospective study. *Burns: Journal of the International Society for Burn Injuries* **30**, 221–223.

van der Marel K, Bouet V, Meurhoff GF, Freret T, Boulouard M, Dauphin F, Klomp A, Lucassen P, Homberg JR, Dijkhuizen RM and Reneman L (2015) Effects of long-term methylphenidate treatment in adolescent and adult rats on hippocampal shape, functional connectivity and adult neurogenesis. *Neuroscience* **309**, 243–258.

Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality, I, Management, Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT and Visser S (2011) ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/ hyperactivity disorder in children and adolescents. *Pediatrics* **128**, 1007–1022.