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ORIGINAL ARTICLE

Treatment with methylphenidate and the risk of fractures among children and young people: A systematic review and self-controlled case series study

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Aims: Animal studies suggest that methylphenidate treatment for around 3 months may lead to less mineralized and weaker appendicular bones. A systematic review was conducted to summarize the evidence from observational studies, and a self-controlled case series study was used to compare the risk before and after treatment initiation.

Methods: Literature search was conducted using PubMed, Embase and the Cochrane Library to identify observational studies on methylphenidate and fractures. We also conducted a self-controlled case series study with individuals aged 5–24 years who received methylphenidate treatment and experienced fractures from 2001 to 2020 in Hong Kong. Incidence rate ratios and 95% confidence intervals were calculated by comparing the incidence rate in the methylphenidate-exposed period compared with nonexposed period.

Results: Six cohort studies and 2 case–control studies were included in the systematic review. For all-cause fractures, studies found a 39–74% lower risk in treated-attention deficit hyperactivity disorder (ADHD) group compared with untreated ADHD but no difference between stimulants and nonstimulants. Differences between sexes and treatment duration were also found—significant results were shown in males and those with longer treatment duration. Among 43 841 individuals with ADHD medication before the year 2020, 2023 were included in the self-controlled case series analysis. The risks of fractures were lower by 32–41% in different treatment periods when compared with 6 months before treatment initiation.

The authors confirm that the PI for this paper is Professor Ian C.K. Wong. This project contains a literature review and a pharmacoepidemiology study without patient contact and, therefore, there is no issue related to direct clinical responsibility for patients.

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Conclusion: Methylphenidate treatment may lower the risk of all-cause fractures from both study designs; however, further evidence is needed about the treatment duration and sex effect. Conclusions on stress fractures are not yet established, and further research is required.

KEYWORDS
clinical pharmacology, drug safety, pharmacoepidemiology, pharmacotherapy, psychopharmacology, psychotropic drugs, systematic review

1 | INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is 1 of the most common neurodevelopmental disorders in children and young people, affecting around 2–7% of children around the world[1] and approximately 6.4% of children in Hong Kong.[2] As the most commonly used ADHD medication in many countries,[3] methylphenidate has been extensively studied on both efficacy and safety[4–6]; however, only a few studies have focused on orthopaedic safety.

Several animal studies and in vitro experiments have shown that methylphenidate treatment may lead to adverse effects concerning bone quality. Komatsu and colleagues[7] found that being treated with methylphenidate for around 13 weeks resulted in smaller, less mineralized and weaker appendicular bones in rats, due to the potential mechanism of inhibition of the weight gain, and effects of sex hormones, such as testosterone, which is crucial to the growth of the pubertal skeleton. Such effects were found to improve after 5 weeks of cessation of treatment. Several other animal studies[8] showed similar results and also suggested potential differential effects with different dosages and sexes.[9,10] For example, some characteristics related to the biomechanical integrity such as energy to failure and stiffness were found to be worse with increased doses of methylphenidate, only in male rats.

Injury and falls account for the majority of fractures that happen in children under 15 years old according to the World Health Organization.[11] Our recent study showed that accidental falls are not uncommon among young people in the general public.[12] Moreover, children and adolescents with ADHD have a higher risk of falls and injury than typically developing children and are therefore more likely to fracture a bone.[13–16] Although previous studies have demonstrated that the use of methylphenidate is associated with a lower risk of injury,[17,18] given the potential negative bone-metabolic effect of methylphenidate, it is not clear if methylphenidate is associated with the risk of fractures. Fractures have a negative impact on children and young people in multiple ways.[19–25] Given the increasing trend of methylphenidate uses all over the world over the past 20 years,[3,26] it is necessary to understand the relationship between the risk of fractures and methylphenidate use, to address the knowledge gap and to provide clinical guidance. Although several observational studies using between-subject design[17,18,27,28] have been conducted to investigate the association between the use of methylphenidate and the risk of fractures, they have yielded mixed results.

What is already known about this subject

- Prior animal research indicates that methylphenidate exposure may alter bone composition in rats. Despite observational human studies examining the relationship between methylphenidate use and fracture risk, no conclusive evidence exists as systematic investigations in real-world clinical settings are lacking. Furthermore, population-based studies only compared risk between treated and untreated individuals, possibly introducing bias due to baseline characteristics.

What this study adds

- A systematic review of population evidence using between-individual designs revealed a general association between methylphenidate use and decreased fracture risk. Our original study employing within-individual comparisons also demonstrated a reduced risk following methylphenidate initiation. The results suggest that the advantages of methylphenidate treatment in preventing trauma or injury-induced fractures may surpass the risks associated with changes in bone quality in humans.

According to our preliminary search on the association between methylphenidate use and the risk of fracture, we found that most of the current studies were comparing the risk in treated-ADHD with nontreated ADHD or non-ADHD. However, there is some residual confounding due to different characteristics between the comparison groups. Therefore, we also hope to explore the changes in fracture risk after methylphenidate uses through within-individual comparison.

To obtain comprehensive evidence, we aimed to use 2 designs—a systematic literature review and a population-based study of within-individual comparison with explore whether methylphenidate treatment increases the risk of fractures in children and young people.

2 | METHODS

2.1 | Design 1—systematic literature review

Two authors (L.G. and G.G.) conducted the literature search of PubMed, Embase and the Cochrane Library from inception through 28 July 2021 using the search terms listed in Appendix S1.

Titles, abstracts and full text were assessed by 2 authors (L.G. and G.G.) to identify analytical observational studies. The inclusion criteria were as follows:

1. Population: individuals of any age;
2. Intervention: methylphenidate;
3. Outcome: fractures, any type;
4. Study design: observational studies;
5. Language: English.

Case reports and animal studies were excluded. We then extracted information including study characteristics (the first author, publication year, country/region), participant details (inclusion/exclusion criteria, age, data source, sample size) and reported outcomes (metrics such as the adjusted incidence rate ratio [IRR], hazard ratio [HR], odds ratio [OR], rate ratio [RR] and the corresponding 95% confidence intervals [CI]).

Data syntheses were conducted based on the number of included studies. Due to the limited number of studies, we did the formal narrative synthesis by summarizing the detailed information in the forest plot (including the sample size and characteristics of the study group and control group, the effect size and the 95% CI) of each study using Excel. Data synthesis was conducted by 2 reviewers independently (L.G. and G.G.) and triple-checked by another reviewer (M.F.).

Included studies were assessed for methodological quality using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool[29] by 2 authors (L.G. and G.G.). The overall risk of bias can be Low, Moderate, Serious or Critical based on the assessment of the domains of Bias due to confounding, Bias in selection of participants into the study, Bias in classification of interventions, Bias due to deviations from intended interventions, Bias due to missing data, Bias in measurement of outcomes and Bias in selection of the reported result. Disagreements were settled by another senior reviewer (K.K.C.M.).

This study was registered with the International Prospective Register of Systematic Reviews (reference no. CRD42021290986) and was reported based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist[30] (Appendix S2).

2.2 | Design 2—within-individual comparison

We conducted a self-controlled case series study, which is used to compare the incidence of the event of interest, during the exposure period(s) with that in the nonexposure period(s).[31] As it is based on the within-individual comparison, where all participants act as their own control, all time-invariant confounders that vary between individuals are controlled implicitly, therefore, can eliminate selection bias that arises from the difference between individuals that exists in cohort or case–control studies.[32,33] In the primary self-controlled case series analysis, we divided the individual observation period into 6 mutually exclusive risk windows: 6 months before the first prescription, exposure periods within 6 months of the first prescription, exposure periods within 7 to 12 months of the first prescription and periods of subsequent exposure) and 1 reference window (other nonexposure periods; Figure 1), to assess the association between

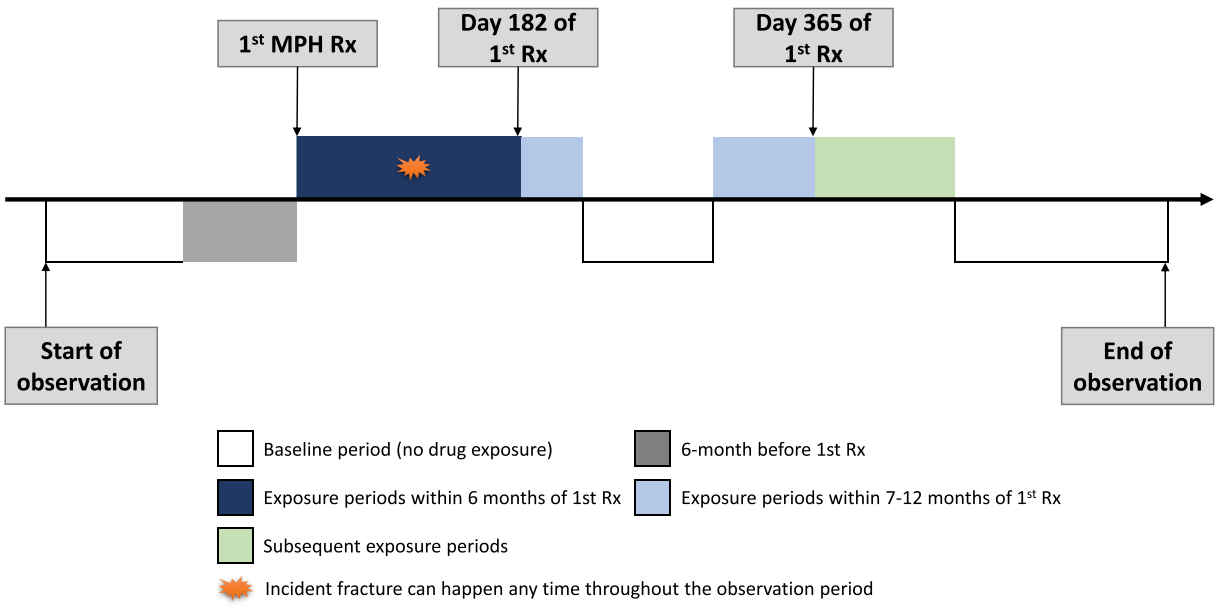


FIGURE 1 Illustration of the primary self-controlled case series analysis. rx, prescription.

methylphenidate treatment and the risk of fracture. The pre-exposure period is set up to avoid the violation of the assumption that the outcome of interest should not influence the probability of having the exposure.[31] To further investigate the changes in the fracture risk during the observation period, the spline-based self-controlled case series analysis was also performed.

The study protocol has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference no. UW 12-136).

2.2.1 | Database

The data we used in this study come from the Clinical Data Analysis and Reporting System (CDARS). It is an electronic database created by the Hong Kong Hospital Authority, the sole public health service provider in Hong Kong with services available to all 7.3 million Hong Kong residents. The database includes prescription, dispensing, diagnosis and other electronic medical records (EMRs) from all public hospitals and clinics, including inpatient, outpatient and accident and emergency departments. Data from CDARS have been used in various pharmacoepidemiological studies, including studies on ADHD[34,35] and methylphenidate.[26,36–38]

2.2.2 | Population

Children and young people aged between 5 and 24 years with both methylphenidate prescription and incident fracture during January 2001 and December 2020 were included in the analysis. The individual observation started on 1 January 2001, date of the first record in CDARS, or the 5th birthday, whichever was latest, and ended on 31 December 2020, 1 day before the 25th birthday, first prescription date of other ADHD medication (atomoxetine or lisdexamfetamine) or the registered date of death, whichever was earliest.

2.2.3 | Exposure

The exposure periods were obtained directly from the prescription records in CDARS. In the event where the prescription duration is missing, we calculated it by the prescribed quantity, frequency and strength. Median imputation was used for the remaining missing duration, which occupies only a small proportion (0.15%).

2.2.4 | Outcome

To comply with the self-controlled case series assumption that recurrent outcome events are independent, we studied only the first event in the analysis.[31] The incident fracture case was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 800 to 829.

2.2.5 | Statistical analysis

IRRs and 95% CIs of the outcome during different risk windows compared with the reference window were calculated using conditional Poisson regression. Age of 1-year age band, season (cut-off points: 1 March, 1 May, 1 September and 1 November) and the coronavirus disease 2019 (COVID-19) stringency index[39] were controlled for in the analysis (Figure S1). A *P*-value <.05 was considered as statistically significant.

We also performed additional analyses to prove the robustness of our results. In the subgroup analysis, we analysed according to sex, the type of fracture, cumulative treatment duration and incident methylphenidate user. In addition, we identified the nontraumatic fractures to evaluate the potential effect of methylphenidate use on the bone quality. We also selected incident diseases of oesophagus, stomach and duodenum (ICD-9-CM: 530-539) as the negative control outcome to prove the reliability of the self-controlled case series method. In the sensitivity analysis, we redefined the risk window or the observation period and also used the fall as the outcome to study the potential risk of fragility fractures after the methylphenidate treatment. The details for all the subgroup and sensitivity analyses are shown in Appendix S3.

Microsoft Excel and R v3.6.1 were used for data analysis. L.G. and K.K.C.M. conducted the initial data analyses, and MF cross-checked the analyses independently for quality control.

3 | RESULTS

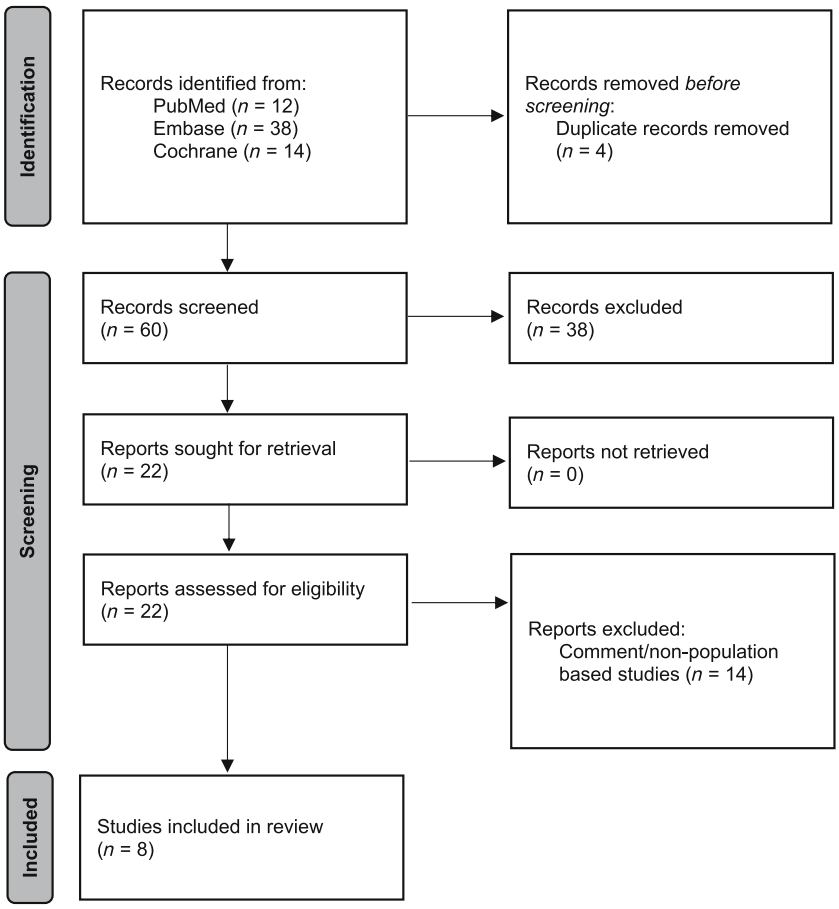
3.1 | Design 1—systematic literature review

Sixty-four records were retrieved from PubMed, Embase and the Cochrane Library, after removing duplicate records and records that did not meet the inclusion criteria; 8 studies with available full text were included in the systematic review (Figure 2).

Information of the included studies is listed in Table S1. These studies were published between 2018 and 2022, with 4 of them from Israel, 2 from the USA, and 1 each from Taiwan and Germany. There are 6 studies using cohort study design (3 on fractures, 2 on stress fractures, and 1 on stress and traumatic fractures) and 2 studies using case–control study design (one on fractures and 1 on stress fractures). For the ROBINS-I assessment, most of the 8 studies showed Serious risk of bias due to the inadequate adjustment of important confounders (Table S2).

For the outcome of fractures (Figure 3), 1 cohort study[28] found a significantly lower risk of clinical relevance in the ADHD treatment group compared with ADHD without treatment group (HR 0.26, 95% CI 0.17–0.38), but no difference between medication type (stimulants or nonstimulants), while another cohort study conducted by Chen and colleagues[40] found a significantly lower risk only in the group treated with methylphenidate for more than 180 days. Schermann and colleagues[41] found a higher risk of fractures in nontreated ADHD individuals when compared with non-ADHD individuals. In addition, they

FIGURE 2 Flow chart of systematic review.



Study type	Study ID (Ref#)	Exposure group	Sample size	Adjusted estimates (95% CI)	Adjusted estimates (95% CI)
Cohort	Perry BA 2016	ADHD with treatment	5696		HR 0.26 (0.17-0.38)
		ADHD without treatment	4369		–
		ADHD treated with stimulant	5268		HR 0.92 (0.60-1.40)
		ADHD treated with non-stimulant *	428		–
	Chen VC 2017	ADHD treated with MPH for 1-180 days	1742		HR 1.18 (0.98-1.43)
		ADHD treated with MPH for 180+ days	1836		HR 0.77 (0.63-0.94)
		ADHD without treatment *	2623		–
	Schermann H 2018 **				
	Men	ADHD without treatment	6122		OR 1.46 (1.21-1.76)
		ADHD treated with 1-90 tablets MPH	1816		OR 0.74 (0.57-0.95)
		ADHD treated with 91-180 tablets MPH	417		OR 0.53 (0.30-0.94)
		ADHD treated with 180+ tablets MPH	586		OR 0.48 (0.30-0.76)
		Non-ADHD *	400337		–
	Women	ADHD without treatment	4183		OR 1.82 (1.35-2.45)
		ADHD treated with 1-90 tablets MPH	1696		OR 1.23 (0.90-1.67)
		ADHD treated with 91-180 tablets MPH	455		OR 0.88 (0.46-1.67)
		ADHD treated with 180+ tablets MPH	667		OR 0.69 (0.37-1.28)
		Non-ADHD *	263278		–
Case-control	Jacob L 2017	With ADHD treatment	Case: 1447		OR 0.61 (0.51–0.73)
		Without ADHD treatment *	Control: 1447		–

* reference group; ** 95% CI was calculated using P value (https://www.bmj.com/content/343/bmj.d2090).
Abbreviation: ADHD=attention deficit hyperactivity disorder, MPH=methylphenidate, HR=hazard ratio, OR=odds ratio, CI=confidence interval.

FIGURE 3 Results of systematic literature review on fractures.

also found a dose–response relationship that higher dose of methylphenidate was associated with a lower risk of fracture. However, the effect was only observed in males. One case–control study[42] also detected a lower risk in the ADHD medication treatment group compared with the nontreatment group (OR 0.61 95% CI 0.51–0.73; Figure 3).

Several studies focused on stress fractures or traumatic fractures (Figure S2). Ben-Ami and colleagues[27] found increased risks in the ADHD treated group compared with non-ADHD individuals (adjusted OR 1.04, 95% CI 1.02–1.07); however, opposite findings were found in another study[43] with the treatment of methylphenidate at lower risk of stress fractures compared with non-ADHD group (adjusted OR 0.64, 95% CI 0.51–0.81). Schermann and colleagues[44] focused on the dose–response effect and showed that when compared with non-ADHD individuals, although the overall estimates of the stress fracture risk in the methylphenidate users are all lower than 1, significantly lower risk was only detected in females with the highest dose of treatment (total medication >180 tablets). Another case–control study[45] by Schermann and colleagues found an increased risk of stress fractures associated with methylphenidate treatment.

3.2 | Design 2—within-individual comparison

A total of 43 841 individuals with ADHD medication prescriptions before 2020 were identified in CDARS; 2023 with both methylphenidate and incident fracture were included in the self-controlled case series analysis (Figure S3). Among these 2023 individuals, 88.24% were male (Table 1), 80.28% had an ADHD diagnosis and over 90% had at least 1 psychiatric comorbidity (Table S3). Detailed information on baseline characteristics and follow-up information are shown in Table 1 and Table S3.

In the primary self-controlled case series analysis (Table 2), we found a significantly higher risk of fracture in the 6 months before methylphenidate initiation compared with the baseline period (IRR 1.27, 95% CI 1.05–1.53), a similar but imprecise risk to the baseline period in the 7–12 months after treatment initiation (IRR 0.75, 95% CI 0.56–1.02) and in periods within 6 months since methylphenidate initiation (IRR 0.77, 95% CI 0.59–1.00) and subsequent exposure period (IRR 0.87, 95% CI 0.75–1.00). When compared with the 6-month pre-exposure period, the risk of fractures was decreased by 39% (IRR 0.61, 95% CI 0.45–0.82) in the first 6 months after methylphenidate initiation, 41% (IRR 0.59, 95% CI 0.42–0.84) in the 7–12 months after treatment start and 32% (IRR 0.68, 95% CI 0.55–0.85) during the subsequent exposure period. A similar result was observed in the spline-based self-controlled case series (Figure S4). Negative control outcome analysis did not detect any significant risk of diseases of oesophagus, stomach and duodenum (Table 2 and Table S4).

The sex-stratified analysis resulted in a similar pattern to the primary analysis in both sexes (Table S4). Subgroup analyses of appendicular fractures, different treatment duration and incident users showed similar risk patterns to the main analysis. When limiting the outcome to nontraumatic fractures, we still observed a decreased risk of nontraumatic fractures after treatment initiation, compared with 6 months before the treatment, and the risk was significantly lower in the subsequent exposure period (IRR 0.52, 95% CI 0.30–0.91).

For the sensitivity analysis, when changing the observation start date for people with ADHD to the first ADHD diagnosis or ADHD medication prescription date, the risk of fracture in different risk windows after treatment was similar to the baseline level and the pretreatment period. The other sensitivity analyses showed robust results with the primary analysis (Table S5 and Figure S5).

4 | DISCUSSION

The systematic literature review identified and summarized 8 cohort studies and case–control studies all using between-individual comparisons with limited study quality. The risk of all-cause fractures was reported to be generally lower in the treated ADHD groups, than in the untreated ADHD groups; however, this potential protective effect became weakened or even nonsignificant with shorter treatment duration studies and in females. Studies have shown that nontreated ADHD is associated with poorer physical, psychosocial and social function outcomes, compared with treated groups.[46–48] Thus, the lower risk of all-cause fractures in treated ADHD groups could be explained by the protective effect of reducing trauma and injury[17,18] through more effective control over the core ADHD symptoms, particularly impulsivity. Two studies[40,41] used the total tablets of ADHD medication prescribed or treatment duration to categorize the exposure group and found that the risk decreased with a longer treatment period; however, this trend failed to reach significance in females. This might be because of sex differences in ADHD symptoms, which may need further studies. Females traditionally report lower levels of impulsivity,[49,50] differential treatment efficacy[51] or sex differences in baseline risk of fractures.[41]

TABLE 1 Baseline characteristic of self-controlled case series analysis.

	No. of patients (%)	Mean (SD) age at baseline (years)	Median (IQR) daily dosage (mg)	Median (IQR) length of prescription (days)	Exposed period		Unexposed period	
					No. of events	Follow-up time (patient-years)	No. of events	Follow-up time (patient-years)
All	2023 (100)	5.65 (1.70)	10 (10–20)	83 (48–111)	465	5618.68	1558	19 011.99
Male	1785 (88.24)	5.67 (1.72)	10 (10–20)	83 (48–111)	425	5020.88	1360	17 035.43
Female	238 (11.76)	5.46 (1.47)	10 (10–20)	90 (49–111)	40	597.80	198	1976.56

Abbreviations: IQR, interquartile range; SD, standard deviation.

TABLE 2 Results of primary self-controlled case series analysis and negative control outcome analysis.

Risk window	Number of events (patient-year)	Crude incidence (per 100 patient-year)	IRR[a] (95% CI)	*P*-value
Primary analysis on incident fracture ($n = 2023$)				
6 months before treatment	128 (968.39)	13.22	1.27 (1.05–1.53)	.01
Period within 6 months since first rx	62 (765.34)	8.10	0.77 (0.59–1.00)	.05
Period within 7–12 months since first rx	46 (583.62)	7.88	0.75 (0.56–1.02)	.07
Subsequent treatment	357 (4269.72)	8.36	0.87 (0.75–1.00)	.05
No methylphenidate	1430 (18 043.61)	7.93	1.00 (–)	--
Direct comparison between methylphenidate treatment and 90 days before treatment				
Period within 6 months since first rx	62 (765.34)	8.10	0.61 (0.45–0.82)	<.01
Period within 7–12 months since first rx	46 (583.62)	7.88	0.59 (0.42–0.84)	<.01
Subsequent treatment	357 (4269.72)	8.36	0.68 (0.55–0.85)	<.01
6 months before treatment	128 (968.39)	13.22	1.00 (–)	--
Negative control analysis with diseases of oesophagus, stomach and duodenum (ICD-9-CM: 530–539) as outcome ($n = 1008$)				
6 months before treatment	48 (481.60)	9.97	0.91 (0.67–1.23)	.54
Period within 6 months since first rx	37 (378.04)	9.79	0.97 (0.69–1.37)	.85
Period within 7–12 months since first rx	31 (289.37)	10.71	1.15 (0.79–1.68)	.47
Subsequent treatment	135 (2048.10)	6.59	0.94 (0.75–1.19)	.63
No methylphenidate	757 (8343.24)	9.07	1.00 (–)	--
Direct comparison between methylphenidate treatment and 90 days before treatment				
Period within 6 months since first rx	37 (378.04)	9.79	1.06 (0.69–1.64)	.78
Period within 7–12 months since first rx	31 (289.37)	10.71	1.27 (0.80–2.00)	.31
Subsequent treatment	135 (2048.10)	6.59	1.04 (0.73–1.48)	.83
6 months before treatment	48 (481.60)	9.97	1.00 (–)	--

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; rx, prescription.

[a]All estimates were adjusted for age in 1-year age band and seasonal effect and COVID-19 stringency index using conditional Poisson regression, with a significance level of 5% for a 2-tailed test.

For stress fractures, there are several discrepancies in the findings. One study[27] found a marginally higher risk in ADHD with methylphenidate treatment compared with non-ADHD, whereas another study[43] found a lower risk. This may be because patients in the treated group were relatively young; therefore, they may have different responses in bone growth compared with adults and their own risk of stress fractures is relatively low. For males receiving treatment, the risk was significantly reduced compared with nontreated ADHD and non-ADHD. However, in females, the protective effect of reduction in stress fractures was found only in the long-term treatment group, and the protective effect did not tend to expand over the treatment duration. In general, these results in humans do not confirm the animal experiments, which show that methylphenidate may have an adverse effect on bone quality. Therefore, there is not yet sufficient evidence to support that the use of methylphenidate increases the risk of stress fractures in humans.

For the between-individual design studies that make comparisons between an exposed group and a nonexposed group, the findings may be affected by residual confounding as individuals receive treatment with a reason; in that case, the comparability between the exposed and control groups has become a major issue in the interpretation of the results. However, our self-controlled case series analysis with within-individual comparison resulted in an observed overall lower risk of all-cause fractures after the initiation of methylphenidate. This methodology accounts for many of the potential confounders in between-individual studies. In our view, these findings are most likely to be explained by the prevention of trauma,[17] thus reducing the risk of fractures and stress fractures as an indirect effect of treatment. Such benefits from trauma prevention may outweigh the risk of fragility fractures due to fall or nontraumatic fractures due to the methylphenidate-induced problems on bone quality. As a result, of the preventative effect due to methylphenidate treatment, a lower risk of overall fracture is observed. Currently, we do not have adequate human data to understand the effects of methylphenidate on bone quality it would, however, appear that from a risk–benefit perspective, even if methylphenidate would lead to changes in bone quality, the prevention of trauma and injury may still lower the risk of fracture in patients with ADHD. These effects look similar when splitting the individuals by sex or cumulative treatment duration (<1 year and ≥1 year). Due to the limited sample size, we were not able to evaluate the effect on stress fractures. In Hong Kong, among 43 841 individuals who received at least 1 ADHD medication prescription in the

past 20 years, only 15.7% of them had prescription records in their adulthood with a median age of only 24 years. Very few records of stress fractures were found in the EMRs among this group of individuals. Therefore, further studies are needed to explore the risk of methylphenidate use and stress fractures.

There are several strengths of our study. Firstly, we systematically summarized current evidence on the treatment using methylphenidate and the risk of all-cause fractures and stress fractures. Secondly, to improve on the existing studies, we conducted a self-controlled case series study to compare the risk of fractures within patients who received methylphenidate treatment using territory-wide population-based data. Whereafter, in the self-controlled case series study, we adjusted time-varying confounders including age, season and COVID-19 and also conducted several sensitivity analyses to prove the robustness of the primary self-controlled case series analysis.

However, the findings of this study need to be interpreted with the following limitations. For the systematic literature review, due to the methodological discrepancies among the previous studies, it is difficult to meta-analyse the results to provide the overall estimate. For the self-controlled case series study, similar to many other studies[26,37] using CDARS data, our study population is based only on EMRs from public settings. However, based on existing research,[52] we believe that the vast majority of children and adolescents with chronic disorders such as ADHD would go to public hospitals for treatment and most fractures are identified in the public system. In addition, using EMRs, we could only use the diagnosis of fractures as the outcome, instead of the examination of the bone quality, such as the geometry and microarchitecture of bone from computed tomography scans and magnetic resonance imaging.

Our study shows that for all-cause fractures, the results of the between-individual comparison and within-individual comparison demonstrated that the use of methylphenidate is associated with lower risk, whether compared with the nontreated group or with the period before the treatment initiation. However, further evidence is needed about the treatment duration and sex effect.

AUTHOR CONTRIBUTIONS

Le Gao, Kenneth K.C. Man and Ian C.K. Wong designed the study. Le Gao and Grace M.Q. Ge independently did the literature search, data extraction, quality assessment and information summary for the systematic review. Le Gao, Kenneth KC Man and Min Fan extracted the data; conducted the statistical analyses; and cross-checked the analyses for the within-individual design. Le Gao and Kenneth K.C. Man wrote the first draft of the manuscript. Wallis C.Y. Lau, Ching-Lung Cheung, David Coghill and Patrick Ip provided critical input to the interpretation of the analysis. All authors contributed to the interpretation of the analyses and the review and editing of the manuscript and approved the submission of the final version.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

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).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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