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ORIGINAL CONTRIBUTION

Increased risk of developing psychiatric disorders in children with attention deficit and hyperactivity disorder (ADHD) receiving sensory integration therapy: a population-based cohort study

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Abstract

Parents of children with attention deficit hyperactivity disorder (ADHD) have been found to prefer sensory integration (SI) training rather than guideline-recommended ADHD treatment. This study investigated whether SI intervention for children with ADHD was associated with a reduced risk of subsequent mental disorders. From children < 8-years-old newly diagnosed with ADHD in a nationwide population-based dataset, we established a SI cohort and a non-SI cohort ($N = 1945$) matched by propensity score. Incidence and hazard ratios of subsequent psychiatric disorders were compared after a maximum follow-up of 9 years. The incidence of psychiatric disorders was 1.4-fold greater in the SI cohort, with an adjusted hazard ratio of 1.41 (95% confidence interval 1.20–1.67), comparing to the non-SI cohort. Risks were elevated for emotional disturbances, conduct disorders, and adjustment disorders independent of age, gender, or comorbidity. Among children with only psychosocial intervention, the incidence of psychiatric disorders was 3.5-fold greater in the SI cohort than in the non-SI cohort. To our knowledge, this is the first study to report an increased risk of developing psychiatric disorders for children with ADHD who received SI compared to those who did not. Potential adverse effects of SI for ADHD children should be carefully examined and discussed before practice.

Keywords Non-western country · Attention deficit and hyperactivity disorder · Psychiatric disorders · Sensory integration · Conduct disorder · Affective disorder

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Introduction

Attention deficit and hyperactivity disorder (ADHD) is a neurodevelopmental disease that causes serious social or occupational impairments affecting 5% [1, 2] to as high as 20% [3] of school aged children with symptoms of inattention, hyperactivity, or impulsivity [4]. Some cases diagnosed in childhood may continue to have symptoms into adulthood involving behavior disorder and conduct disorder (CD) [5–7]. Furthermore, impairments in academic performances [8], social incompetence [9], and/or conflicting parent–child interactions owing to symptoms [10] may underlie an increased risk of depression. The incidences of bipolar disorder among ADHD children range from 7 to 29% [11–14], with a fourfold increased odds of developing bipolar disorder in ADHD children comorbid with CD or oppositional defiant disorder (ODD).

Previous studies have reported the effectiveness of Methylphenidate (MPH) therapy and psychosocial interventions [15] in the treatment of childhood ADHD [16]. Improvements in ADHD symptoms, such as inattention, hyperactivity, or impulsivity on active treatment, have been observed in children under 8 years of age [17–19]. However, MPH therapy is not recommended for young children (aged under 7) as the first choice of treatment. Most evidences suggest that combinations of parent and/or teacher behavior training, social skills training, as well as multi-model managements are recommended for young children with ADHD [9, 20, 21]. Thus, despite the increased recognition of ADHD, a recent study found that less than 1% of children and adolescents were identified and treated with pharmacological interventions by child psychiatrists [22]. Some of these children were diagnosed but were not adequately treated [23] because of lacking relevant resources. In addition, parents may hesitate to accept medications because the guidelines do not suggest MPH for children under 7-years-old as a first-line treatment due to the potential presence of side effects [21].

Sensory integration (SI) therapy is a therapeutic physical activity developed by A. Jean Ayres for children with autism spectrum disorder, mental retardation, learning disability, emotional disturbance, or self-mutilation [24]. SI uses planned, controlled somatosensory, vestibular, tactile, auditory, or proprioception inputs to enhance children's attention, state of arousal, and sensitivity to environmental stimuli [24–26]. Parents of children with ADHD may seek for other therapy such as SI therapy to modulate or improve their children's attention, behaviors, or socialization skills [24–26]. However, the effectiveness of SI therapy is limited and inconclusive because of small sample sizes, variations in intervention dosage [27, 28], poor compliance with intervention, heterogeneous samples [26, 29], or inappropriate selection on research outcome measures [25, 30]. It has been suggested that the clinician ought to discuss with parents of treatment indications and mechanisms, as well as skills for monitoring the effectiveness of the therapy [26].

Because of the non-stigmatizing property of SI and the easy accessibility to occupational therapist with insurance coverage, parents of young children with ADHD may prefer to SI instead of seeking for regular multi-model behavioral managements. This behavior might delay the guideline-indicated ADHD treatment, resulting in subsequent conduct disorders or psychiatric comorbidities. With the advantage of a population-based dataset, this study aimed to elucidate whether applying SI intervention in children with ADHD was associated with reduced or increased subsequent psychiatric disorders.

Methods

Data sources

We identified the study subjects from claims data of the National Health Insurance (NHI), which is a single-payer medical insurance system, providing unrestricted universal health care for all residents in Taiwan [31]. This study used claims data of a random sample of all insured children under 18 years in Taiwan from 1996 to 2008, which was a subset of the National Health Insurance Research Database (NHIRD). This pediatric dataset included general information of age, gender, medical service use, drug prescriptions, and interventions coded with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses coded at each medical service receipt [31]. All personal identifications had been encrypted by the Bureau of NHI before the data were released to the researchers to protect patient confidentiality. The Research Ethics Committee of China Medical University and Hospital approved this study.

Study population

From the claims data, we identified children with attention deficit and hyperactivity disorder [ADHD; ICD-9-CM code: 314.XX, not including 314.1 (hyperkinesis with development delay) and 314.2 (hyperkinetic conduct disorder)] newly diagnosed during the period of 2000–2006 as the study population ($N = 13{,}214$). Children with any diagnosis of psychiatric outcomes (ICD-9-CM code: 290.XX–298.XX, 300.XX–301.XX, 308.XX–313.XX), or hyperkinetic conduct disorder (314.2), before the date of SI treatments (index date), missing baseline data of demographic risk factors, or age over 8 years were excluded ($n = 3803$). Subjects under 8-years-old with ADHD received SI treatments

were identified as SI cohort ($n = 1945$). The SI treatments included coordination training, sensory training, activity therapy, balance training, ADL training and motor sensory training. From the ADHD population, children without SI treatments and history of psychiatric disorders during 2000–2006 were selected as the non-SI cohort, matched by sex, age, and propensity scores. The propensity score was calculated for each child according to sex, age (per 2 years old), urbanization of residential area, parental occupation, comorbidity, ADHD medication used, psychosocial intervention, index year, and year of ADHD diagnosis date. Levels of urbanization were classified into levels 1–7 based on the population density (people/km [2]), proportion of higher education, size of elderly and agricultural populations, and number of physicians per 100,000 people. Levels 6 and 7 were combined into Level 5 because of relatively small numbers. Level 1 represented the highest level of urbanization, whereas Level 5 was the least urbanized.

Our primary outcome was the occurrence of subsequent psychiatric disorders during the follow-up period. Psychiatric disorders were further divided into the affective disorder (ICD-9-CM code: 296), schizophrenia (ICD-9-CM code: 295), psychosis (ICD-9-CM code: 2988 and 2989), conduct disorders (ICD-9-CM code: 312, 314.2), emotional disturbances (ICD-9-CM code: 313), personality disorders (ICD-9-CM code: 301), anxiety disorders (ICD-9-CM code: 300), and adjustment disorder (ICD-9-CM code: 309). ADHD children may have more than one psychiatric diagnosis. These diagnoses represented all treated conditions since appropriate diagnoses are required in the NHI system for any medical intervention given.

We calculated the follow-up time in person-years for each participant from the index date until the diagnosis of psychiatric disorder, the end of 2008, or withdrawal from the insurance system (because of death or loss to follow-up). We also identified the history of comorbidity for each child before the end of follow-up such as autism (ICD-9-CM code: 299), hyperkinesis with development delay (ICD-9-CM code: 314.1), specific delays in development (ICD-9-CM code: 315), mental retardation (ICD-9-CM code: 317–319), cerebral palsy (ICD-9-CM code: 343 and 344), hearing loss (ICD-9-CM code: 388) because these are therapeutic indications for SI treatment. These disorders are indications of the severity of mental and physical health status, which might be associated with our outcome. ADHD children receiving psychosocial interventions before the end date was calculated for adjustment because these interventions might help preventing subsequent psychiatric disorders from happening. We also evaluated the incidence and hazard ratios of psychiatric disorders associated with and without psychosocial intervention and ADHD medications. We considered not only those potential risk factors, but also conditions of ADHD medication usage before the end date in SI and non-SI cohorts, including concerta, ritalin, and strattera. We calculated the average daily dose by fractions of cumulative doses divided by cumulative exposure days (or 'days supply') [32] using 'Defined Daily Dose' (DDD) [33], which is the average maintenance dose per day for a drug used for its main indication for adults. Median value was used to express the dose of three ranges.

Statistical analyses

We calculated the standardized difference for the distribution of each baseline characteristics between the SI and propensity-matched non-SI cohorts. A difference less than 0.1 was considered as no significant differences. Both cohorts were followed until the psychiatric disorders were identified, or loss to follow-up or the end of 2013 to calculate the incidence rate of psychiatric disorder. Kaplan–Meier proportional cumulative incidences of overall psychiatric disorders were calculated for both cohorts and examined the differences between the two cumulative incidence curves. We used multivariable Cox proportional hazards model to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) of psychiatric disorders for the SI cohort comparing with the non-SI cohort. Incidence rates and aHRs of overall psychiatric disorders were estimated by sex, age groups (age under 4 years and age over 4 years), comorbidity (no/yes), psychosocial intervention treatment (no/yes), and ADHD medication used (no/yes). We also used the Cox method to evaluate the hazard ratio of psychiatric disorders associated with ADHD medication levels, such as cumulative drug dosage, average drug dosage per day and average drug dosage per year. A P value of less than 0.05 obtained through 2-tailed tests was considered statistically significant. All of the data analyses were performed using the SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, USA). Besides, we used R software (R Foundation for Statistical Computing, Vienna, Austria) to conduct the Kaplan–Meier analysis.

Results

After the propensity matching, distributions of sociodemographic status, comorbidities, and intervention and treatment for ADHD were not different between the SI cohort and the non-SI cohort (all $p > 0.61$, indicating no significant differences between two groups, Table 1). Most of ADHD children were boys and children aged 4 years or older. Nearly 60 percent of them did not take ADHD medication.

Figure 1 shows that the cumulative incidence of developing psychiatric disorders was 12.4% greater in patients with SI therapy than those without the therapy (log-rank test p value < 0.0001).

Table 1 Comparison of demographics and comorbidities between ADHD patients receiving sensory integration treatments (SI cohort) and propensity score matched controls (non-SI cohort)

	ADHD children				*p* value
	Propensity score matching				
	Non-SI cohort		SI cohort		
	N = 1945		*N* = 1945		
Variables	*n*	%	*n*	%	
Sex					0.7727
Girls	364	18.7	357	18.4	
Boys	1581	81.3	1588	81.6	
Age, year, mean (SD)[a]	5.80	(1.43)	5.81	(1.34)	0.7950
< 4	227	11.7	217	11.2	0.6141
≥ 4	1718	88.3	1728	88.8	
Urbanization					0.8874
1 (highest)	775	39.9	787	40.5	
2	583	30.0	579	29.8	
3	321	16.5	305	15.7	
4	160	8.23	173	8.89	
5 (lowest)	106	5.45	101	5.19	
Occupation					0.8307
White collar	1301	66.9	1300	66.8	
Blue collar	420	21.6	431	22.2	
Others	224	11.5	214	11.0	
Comorbidity					
Cerebral palsy[b]	2	0.10	4	0.21	0.6873
Autism	121	6.22	116	5.96	0.7375
Hearing loss	40	2.06	40	2.06	1.0000
Delay development	733	37.7	705	36.3	0.3524
Mental retardation	153	7.87	160	8.23	0.6799
Psychosocial intervention					0.4974
No	1391	71.5	1410	72.5	
Yes	554	28.5	535	27.5	
ADHD medication used					0.7623
Non	1140	58.6	1132	58.2	
Only concerta	18	0.93	15	0.77	
Only ritalin	572	29.4	564	29.0	
Only strattera	0	0.00	0	0.00	
Used more 2 types	215	11.1	234	12.0	

Urbanization: level 1 is the most urbanized; level 5 is the least urbanized

White collar: civil services, institution workers, enterprise, business and industrial administration personnel; Blue collar: farmers, fishermen, vendors, and industrial laborers; Others: retired, unemployed, and low-income populations; Chi square test

ADHD attention deficit and hyperactivity disorders, *SI* sensory integration treatments

[a]Student's *t* test

[b]Fisher's exact test

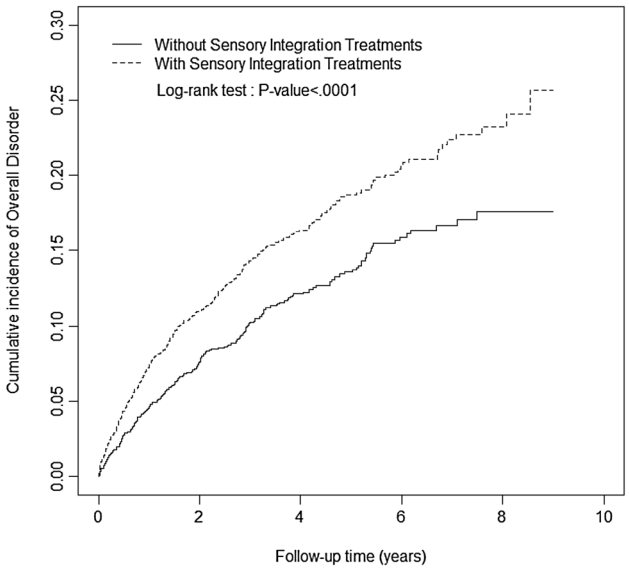

Fig. 1 The cumulative proportional incidence of disorder compared between cohorts with and without sensory integration treatments (dashed line and solid line, respectively) for attention deficit and hyperactivity disorders (ADHD) children

Table 2 shows incidences of overall psychiatric disorders and the adjusted hazard ratios by age, sex, and comorbidity. The incidence of overall psychiatric disorders (including diagnoses of emotional disturbance, conduct disorders, and adjustment disorders) was 41% greater (mainly conduct disorder, emotional disturbances, and adjustment disorders) in the SI cohort than in the non-SI cohort with an adjusted HR of 1.41 (95% CI 1.20–1.67). The disorder incidence was significantly greater in boys than in girls and in younger children than in older children in both cohorts (all $p < 0.001$). Comorbidity was associated with slightly increased incident psychiatric disorders.

For children without both psychosocial intervention and medication, the incident psychiatric disorders were slightly greater in the SI cohort than in the non-SI cohort (Table 3). Incident psychiatric disorders were also greater for the SI cohort receiving ADHD medication, or psychosocial intervention only, or both. The difference between the 2 cohorts was the largest for children receiving only psychosocial intervention (46.9 vs. 13.8 per 1000 person-years) with an adjusted HR of 3.50 (95% CI 1.77–6.91) for the SI-cohort.

Table 4 shows the incidence rates of psychiatric disorders by the average ADHD medication dosage (DDD/day and DDD/year) for both cohorts. The adjusted hazard of psychiatric disorders was significantly higher in the SI cohort than the non-SI cohort in the average ADHD medication dosage of 0.005–0.038 per day (or 2–14 DDD per year).

Table 2 Incidence and SI cohort to non-SI cohort hazard ratio of specific disorder and overall disorders measured by sex, age and comorbidity

Variables	ADHD children						Adjusted hazard ratio[a] (95% CI)
	Non-SI cohort			SI cohort			
	Event	PY	Rate	Event	PY	Rate	
Overall disorder	243	7951	30.6	333	7739	43.0	1.41 (1.20–1.67)***
Affective disorder	9	7951	1.13	14	7739	1.81	1.35 (0.58–3.17)
Schizophrenia	0	7951	0.00	1	7739	0.13	NA
Psychosis	2	7951	0.25	4	7739	0.52	3.18 (0.50–20.1)
Conduct disorders	38	7951	4.78	87	7739	11.2	2.35 (1.61–3.45)***
Impulsive disorder	5	7951	0.63	2	7739	0.26	0.38 (0.07–1.99)
Oppositional defiant disorder	23	7951	2.89	25	7739	3.23	1.13 (0.64–2.01)
Emotional disturbances	48	7951	6.04	84	7739	10.8	1.84 (1.29–2.62)***
Personality disorders	0	7951	0.00	2	7739	0.26	NA
Anxiety disorders	124	7951	15.6	103	7739	13.3	0.86 (0.66–1.12)
Adjustment disorder	10	7951	1.26	22	7739	2.84	2.27 (1.07–4.79)*
Sex							
Girls	33	1494	22.1	53	1462	36.2	1.59 (1.03–2.47)*
Boys	210	6458	32.5	280	6277	44.6	1.38 (1.15–1.65)***
Age, year							
< 4	24	927	25.9	33	845	39.1	1.51 (0.88–2.59)
≥ 4	219	7024	31.2	300	6894	43.5	1.41 (1.18–1.67)***
Comorbidity							
No	149	4609	32.3	180	4659	38.6	1.27 (1.02–1.58)*
Yes	94	3343	28.1	153	3081	49.7	1.67 (1.29–2.16)***

PY person-years, *Rate* incidence rate (per 1000 person-years), *95% CI* 95% confidence interval; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Both groups were matched by propensity scores

[a]Multivariate Cox model controlling for age, gender, comorbidities, psychosocial interventions and drug used. Comorbidity included cerebral palsy, autism, hearing loss, delay development, or mental retardation

Table 3 Incidence and SI cohort to non-SI cohort hazard ratio of overall disorders associated with treatment

Variables	ADHD children						Adjusted hazard ratio[a] (95% CI)
	Non-SI cohort			SI cohort			
	Event	PY	Rate	Event	PY	Rate	
Treatment							
No medication or psychosocial intervention	82	4000	20.5	101	3869	26.1	1.35 (0.99–1.77)
Only ADHD medication used	111	2473	44.9	149	2446	60.9	1.39 (1.08–1.78)**
Only Psychosocial intervention	11	800	13.7	35	746	46.9	3.50 (1.77–6.91)***
Both	39	678	57.5	48	678	70.8	1.27 (0.82–1.96)

PY person-years, *Rate* incidence rate (per 1000 person-years), *95% CI* 95% confidence interval; **$p < 0.01$, ***$p < 0.001$

[a] Multivariate Cox model controlling for age, gender, comorbidities, psychosocial interventions and drug used. Comorbidity included cerebral palsy, autism, hearing loss, delay development, or mental retardation

Discussion

Our study is the first study to show an increased risk of developing psychiatric disorders among children with ADHD who have received SI intervention, compared to those who have not, using a population-based, propensity-matched design for 2 cohorts. The elevated risk appears in both boys and girls, young and older children, and children with or without comorbidity. The risk remains prominent in subgroups with only medication use or only psychosocial interventions. Children under SI intervention receiving ADHD medication or psychosocial intervention only are at a particularly higher risk of psychiatric illnesses.

Table 4 Incidence and SI cohort to non-SI cohort hazard ratio of psychiatric disorder by ADHD medication dosage

Variables	ADHD child						Hazard ratio (95% CI)	
	Non-SI cohort			SI cohort				
	Event	PY	Rate	Event	PY	Rate	Crude	Adjusted[a]
Average drug dosage (DDD/day)								
< 0.005	85	1210	70.3	85	1101	77.2	1.10 (0.81–1.48)	1.09 (0.80–1.48)
0.005–0.038	28	929	30.1	59	1001	58.9	1.91 (1.22—2.99)**	1.79 (1.14–2.83)*
≥ 0.039	37	1012	36.6	53	1022	51.9	1.42 (0.93–2.16)	1.44 (0.94–2.19)
Average drug dosage (DDD/year)								
< 2	83	1184	70.1	82	1031	79.5	1.13 (0.83–1.53)	1.12 (0.82–1.53)
2–14	30	977	30.7	63	1090	57.8	1.84 (1.19–2.85)**	1.76 (1.13–2.74)*
≥ 14	37	989	37.4	52	1003	51.8	1.39 (0.91–2.12)	1.42 (0.93–2.17)

PY person-years, *Rate* incidence rate (per 1000 person-years), *95% CI* 95% confidence interval

$^{*}p < 0.05, ^{**}p < 0.01, ^{***}p < 0.001$

[a] Multivariate Cox model included adjustments of age, gender, comorbidities, psychosocial interventions and drug used. Comorbidity included cerebral palsy, autism, hearing loss, delay development, or mental retardation

Although previous research has reported that CD, affective disorders, and personality disorders are common comorbidities in children with ADHD [6, 7, 9, 10, 12], underlying mechanisms remained uncertain. It is possible that these comorbidities are associated with emotional lability [34], and might relate to developing future depression [35] or bipolar disorders [12]. However, it is compelling to find increased associations between receiving SI and subsequent development of these psychiatric disorders, particularly risks of conduct disorders, emotional disturbances and adjustment disorder are greater for SI children. Of note, in children without any comorbidities significantly raised risk was still observed in the SI group. One might argue that children receiving SI may represent a group of patients with severe behavior disruptions or deficits, possibly not accurately reflected in their diagnoses on claim data (e.g., information regarding ADHD severity were lacking). Consequently, a severe ADHD group receiving SI and a milder ADHD group without any comorbidity might be compared on unequal basis. The generalizability of such a result might be restricted in this SI group of patients and should, therefore, be interpreted with caution. However, even in the stratified subgroup with these comorbidities, the SI cohort still had higher risk of psychiatric disorders than their counterpart. Such finding may depict that SI in ADHD children with comorbidities could not seem to help reduce the risk.

It is important to note that among ADHD children with psychosocial intervention or children with ADHD medications, risks of developing mental illness were significantly greater for children in the SI cohort than in the non-SI cohort. This may imply that severe ADHD cases on psychosocial intervention alone or in combination with pharmacotherapy could not reduce the hazard for the SI group.

Our further data analysis showed that significantly higher risks of developing psychiatric disorders appeared in those received SI than those who did not, regardless of dosage in subgroups of patients receiving MPH or Atomoxetine. This might imply a positive correlation between the risk of interest and the severity of ADHD or other comorbidities not identifiable from the claim data when taking 'average dosage' as a proxy of disease severity (higher average dosage means higher dosage being given in a single day). However, it might also mean that these parents are more inclined to have their children taking medications, or that these children have less barriers or more access to receive pharmacotherapy. On the other hand, higher risks observed in the SI group than in the non-SI group are that at the least evident in subjects with the highest cumulative dose, which suggests that long term pharmacotherapy may be more important in preventing further psychiatric disorders than short term high dose therapy.

Of interest are our findings in ADHD medications from Table 4 that the SI cohort to non-SI cohort HR of developing psychiatric disorders was significantly elevated for those receiving intermediate cumulative or average dosage of medications. This finding demonstrated that the impact of SI is not strong enough during the earlier period with low dose medication. The highest medication dosage does not increase the treatment effectiveness for the non-SI cohort.

However, it is unlikely that SI is associated with psychiatric disorders developed later, as some studies have also reported that ADHD with comorbidities might be distinctive subtypes [36]. Parents may incline to seek other types of treatment instead of guideline-indicated managements provided by child psychiatrists due to the stigma of mental illness [37], or because of a fear of medication-associated side effects or invasiveness [38–41]. However, parents should be

advice that, without behavioral managements and pharmacotherapy, SI therapy alone may lead to frustration in parents due to ineffectiveness.

Strengths of this study include the high level of statistical power to detect associations of interest utilizing detailed records on medical interventions from a large prospective sample of children with clinically diagnosed ADHD. In addition, all information on medical utilization comes from a healthcare system with near-universal coverage and the information is, therefore, nationally representative. Between-group confounding effects were lessened through applying the method of propensity matching. Key limitations are, first, that the diagnoses we obtained were drawn from administrative datasets which might not necessarily generalize to research diagnostic criteria, and may underreport true ADHD or cases with mental illnesses. Although this could be regard as a compensating advantage in the reflection of naturalistic clinical environment, we still purposely chose a relatively broad and unambiguous study category to minimize the bias. Second, although we were able to obtain and adjust for some confounders, information including other basic demographic characteristics, possible risk factors of developing mental illnesses (e.g., stressful events or parent characteristics), severity of ADHD, or other different characteristics between children with and without SI therapy, was not available in the claims data. Third, we have tried to balance differences in comorbidity between the SI and the non-SI groups using propensity matching. This matching process has obtained two balanced cohorts, similar with regards to demographic and clinical characteristics, including comorbidity and treatments, such as autism, hearing loss, or delayed development. Although there might still be other confounding by indications—e.g., children with autism or other indications were more likely to receive SI, it is likely the residual confounding variables was minor and would not affect the findings. Fourth, it is important to bear in mind that the generalizability of this study is limited to children with ADHD receiving medical services, and therefore, those who were not attending clinically might have been missed.

Our results suggest that SI might not be helpful in children with ADHD, especially in those without any identifiable comorbidities. However, as indicated in our findings, psychosocial interventions and pharmacotherapy may be more helpful than SI in preventing future psychiatric disorders. Therefore, perhaps explanations about the benefit of multimodal treatments for ADHD [19] to pediatricians and occupational therapists are needed to increase their referrals. Psychoeducation regarding the effectiveness of behavior management strategies, including combinations of parent, teacher, and social skills training for ADHD children should be provided [19] to parents or care givers bringing their children to receive SI. Further research exploring possible mechanisms of preventing psychiatric disorders in ADHD children with severe comorbidities or in those identified at a very young age; as well as seeking the best model of care are still needed. Finally, efforts to decrease stigmatization [42] and government policies confining insurance payments to guideline indicated interventions [42, 43] instead of reimbursing for the less recommended therapy should also be considered. To conclude, there is a need to clarify possible mechanisms between ADHD receiving solely SI and the risk of subsequent neuropsychiatric disorders; as well as to reconsider the unmet need of proper treatments for ADHD children during their earlier days.

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Author contributions Authors RFT, YCC, KLK, YCW, and SIW designed the study and wrote the protocol. Authors YCW, CHM, and SIW undertook the statistical analysis, and author RFT wrote the first draft of the manuscript. All authors contributed to the writing and have approved the final manuscript.

Compliance with ethical standards

Conflict of interest RS has received research funding in the last 5 years from Roche, Janssen and GSK. All other authors declare that they have no conflicts of interest.

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