Prenatal Paternal Selective Serotonin Reuptake Inhibitors Use and Risk of ADHD in Offspring

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abstract

OBJECTIVES: It has been shown that maternal prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) may be a risk factor for attention-deficit/hyperactivity disorder (ADHD) in offspring. Our goal was to examine whether paternal SSRI use before conception increases the risk of ADHD in offspring.

METHODS: On the basis of Danish national registers, we conducted a cohort study of 781 470 singletons born between 1996 and 2008 with follow-up throughout 2013. The children whose fathers used SSRIs during the last 3 months before conception were identified as the exposed. Cox regression was used to estimate the hazard ratio (HR) of ADHD.

RESULTS: A total of 7216 children (0.92%) were born to fathers who had used SSRIs during the last 3 months before conception. There were 12 520 children diagnosed with ADHD. Compared with unexposed children, the exposed had a 26% increased risk of ADHD (HR = 1.26, 95% confidence interval [CI]: 1.06–1.51) after adjusting for potential confounders. When extending the exposure window to 1 year before conception, paternal use of SSRIs only during the period of 12 to 3 months before conception was associated with the HR of 1.35 (95% CI: 1.10–1.66), whereas paternal use of SSRIs only during the last 3 months before conception was associated with a similarly increased risk of ADHD (adjusted HR = 1.31, 95% CI: 0.95–1.82).

CONCLUSIONS: The mildly increased risk of ADHD in offspring associated with paternal SSRI use before conception could probably be due to the underlying indications related to SSRI use.

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WHAT'S KNOWN ON THIS SUBJECT: Recent studies have shown that certain pharmacological agents used by fathers before conception may increase the risk of adverse neonatal outcomes in offspring. However, little is known about the effect of paternal use of selective serotonin reuptake inhibitors (SSRIs).

WHAT THIS STUDY ADDS: The mildly increased risk of attention-deficit/hyperactivity disorder in offspring associated with paternal SSRI use before conception could probably be due to the underlying indications related to SSRI use.

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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children, characterized by a persistent pattern of inattention and/or hyperactivity impulsivity.[1] A more recent systematic review reported that the estimated worldwide prevalence of ADHD in children and adolescents was 3.4%.[2] Children with ADHD have functional impairments and can experience long-term adverse outcomes, such as conduct disorder, antisocial behavior, and drug abuse.[3] Moreover, this disease exerts a serious financial burden on affected families and society[4] and has been recognized as a major public health problem worldwide.

Both genetic and environmental factors may be implicated in the development of ADHD, but its etiology remains unclear.[5] There is a growing body of literature documenting a wide variety of prenatal factors associated with an increased risk of ADHD (including maternal smoking, stress, alcohol and substance misuse, and exposure to environmental toxins during pregnancy).[6,7] However, few researchers have examined the potential role of paternal factors in the development of ADHD. The hypothesis of an increased risk of developmental defects associated with paternal exposures is not new. For decades, researchers in animal studies have shown that paternal exposure to a broad range of xenobiotic agents may induce reproductive and developmental abnormalities in the offspring (eg, congenital malformations, growth retardation, neurobehavioral deficits, or carcinogenesis).[8–12] Researchers in human studies have also observed that certain pharmacological drugs used by fathers might increase the risk of adverse pregnancy outcomes, birth defects, or childhood cancers.[13–15] The potential mechanisms behind the man-mediated effects have been proposed, including genetic or epigenetic changes with direct disturbances in spermatocytes, and indirect effects by transmission of the xenobiotic agents to the woman via seminal fluid.[8,10]

Recently, prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) has been linked to the risk of several neurodevelopmental disorders in children.[16] SSRIs are widely prescribed for the treatment of depression and other anxiety-related disorders, and their use is increasing.[17–19] Studies in Nordic countries and the Netherlands have shown that one-third of the fathers had used at least 1 drug during the last 6 months before conception,[20] and ~1.4% of fathers were dispensed SSRIs during the last 3 months before conception.[21] Researchers in several human studies have demonstrated that SSRIs could induce semen quality impairment and abnormal sperm-DNA fragmentation,[22–24] which have been reported to be associated with diminished fertility, adverse pregnancy outcomes (like pregnancy loss), and an increased risk of disease in offspring, including childhood cancer.[25] In the most recent rodent study, SSRI administration to male rats adversely affected reproductive performance as well as fetal outcome (including weight gain, organ weights, and feed consumption).[26] However, there is no human evidence for the association between paternal SSRI use before conception and the risk of ADHD in offspring. In this study, we examined the risk of ADHD in children whose fathers used SSRIs during the last 3 months before conception, using data from nationwide Danish health registries.

METHODS

We conducted a nationwide cohort study based on the linkage of several national registers in Denmark. All residents in Denmark are assigned a unique personal identification number, which enables accurate linkage of national registries at the individual level.[27] Secondary data were retrieved by using encrypted identification numbers, and all analyses were performed at the secure platform of Statistics Denmark; thus, there was no access to the personal identification numbers of the participants. The Danish Data Protection Agency approved this project (record no. 2013-41-2569).

Study Population

We identified all singletons born alive in Denmark from January 1, 1996, to December 31, 2008, in the Danish Medical Birth Registry (DMBR). The DMBR contains records of all deliveries in Denmark since 1973 and includes information on gestational age at birth from 1978.[28] A total of 817 842 singletons were identified during the study period. We excluded 20 349 children for whom we could not identify their fathers, 74 children without information on their mothers, 208 children without information on their mothers' parity, 485 children who had missing or extreme values of gestational age (≤23 or ≥45 weeks), and 15 256 children who died or emigrated before 3 years of age. Finally, 781 470 children were included in the analysis.

Paternal SSRI Use

From the Danish National Prescription Registry, we obtained information on paternal SSRI use before conception. Since 1995, this registry has recorded all redeemed prescriptions in Denmark with the following information: the civil registration number of the patient, the dispensing date, the medication code (the World Health Organization's Anatomic Therapeutic Chemical Classification System), the number of packages

prescribed, and the number of dose units in each package.[29] SSRI use was identified on the basis of the Anatomic Therapeutic Chemical code N06AB. Because spermatogenesis is estimated to take ~74 days,[15] we defined the susceptible exposure period as the last 3 months before conception. Accordingly, a child was considered exposed if the dispensing date fell within the specified exposure window or the number of days for which the SSRIs were supplied overlapped with the exposure window. Children born to fathers who had no prescriptions for SSRIs and no supply overlap during the entire exposure window were considered unexposed. For further analyses, we extracted data on paternal SSRI use during the last 1 year before the conception of the index pregnancy and data on maternal SSRI use during the index pregnancy.

ADHD

Using the Danish Psychiatric Central Research Register (DPCRR) and the Danish National Patient Register, we identified children with hospital-based diagnoses of ADHD. The DPCRR contains diagnostic information on every admission from psychiatric hospitals and psychiatric wards in general hospitals in Denmark since 1969 and includes data on all outpatient visits and emergency department contacts since 1995.[30] The Danish National Patient Register has collected data on all inpatients from all somatic hospitals in Denmark since 1977 and outpatients since 1995.[31] The coding classification used during the study period was the *International Classification of Diseases, 10th Revision* (ICD-10). Children with a diagnosis of ADHD (ICD-10 code F90) in the study cohort were defined as case patients. Children were followed up from 3 years of age until the first diagnosis of ADHD, death, emigration, or December 31, 2013, whichever came first.

Covariates

Using the Danish nationwide health registers, we retrieved data on characteristics that may be associated with ADHD in the children or paternal SSRI use. For each child, we obtained information on the calendar year of birth, sex, birth weight, Apgar score at 5 minutes, gestational age, maternal parity, maternal and paternal age at the child's birth, maternal years of education, and maternal smoking status during pregnancy from the DMBR. Parents' psychiatric history before the birth of the child was obtained from the DPCRR by *International Classification of Diseases, Eighth Revision* codes 290-315 from 1977 to 1993 and ICD-10 codes F00-F99 from 1994 and onward. Furthermore, we identified parents diagnosed with affective disorders before the birth of the child (specifically, *International Classification of Diseases, Eighth Revision* codes 296.09, 296.19, 296.29, 296.39, 296.99, 298.09, 298.19, 300.49, and 301.19 and ICD-10 codes F30–F34 and F38–F39).

Statistical Analysis

All analyses were performed by using SAS version 9.1 (SAS Institute Inc, Cary, NC). Cox regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of ADHD in children following exposure to paternal SSRI use before conception.

We adjusted the analyses for the calendar year of birth (1996–1998, 1999–2001, 2002–2004, and 2005–2008), sex of the child (male or female), parity (1, 2, or ≥3), parental age at the child's birth (≤25, 26–30, 31–35, and >35 years), maternal years of education (≤9, 10–14, and >14 years), maternal smoking status during pregnancy (yes or no), maternal history of psychiatric disorders before child's birth (yes or no), and maternal antidepressant use during pregnancy (yes or no) in model 1. We additionally adjusted for paternal history of psychiatric disorders before child's birth (yes or no) in model 2.

To distinguish the direct effect of SSRI use from that of the underlying indication for SSRI use, we extended the exposure window to 1 year before conception and examined the effect of SSRI use before, but not during, the defined 3-month susceptible period. This so-called negative-control strategy allowed us to identify a group of men who used SSRIs only during the period from 1 year to 3 months before conception (former users) and the other 2 groups of men who used SSRIs during the 3-month susceptible period: those who used SSRIs only during the 3-month susceptible period (current users) and those who used SSRIs both before and during the 3-month susceptible period (both former and current users). The reference group consisted of those children born to fathers who did not use SSRIs at any time in the last 1 year before conception. Considering that spermatogenesis happened during 3 months before conception, the ADHD risk observed among the former users could reflect the effects of underlying indication rather than the SSRI use itself.

Stratified analysis was performed to examine whether the association between paternal SSRI use and ADHD in children differed by sex. Considering the potential role of maternal antidepressant medication use as well as maternal mental health during pregnancy in offspring's neurodevelopment, we restricted the analyses to the children whose mothers neither received antidepressants during pregnancy nor had affective disorders. To further distinguish the effect of SSRI medication from that of the main indication (ie, affective disorders),

we performed stratified analyses according to paternal history of affective disorder before the birth of the child. As for those children born to fathers with affective disorders, the ADHD risk we examined could be solely attributable to paternal SSRI use.

To control for unmeasured family-related confounding factors, we conducted a sibling study by including only families with multiple children born in our study period and with at least 1 child with paternal SSRI preconception exposure. We then compared exposed siblings to unexposed siblings to estimate the association between paternal SSRI exposure and ADHD in children.

Considering that there were significant differences among the baseline characteristics of the exposed group and unexposed group, we further created a propensity score–matched (PSM) subcohort to reduce the potential selection bias. The propensity scores were estimated by using logistic regression as the probability of paternal SSRI exposure given some of the baseline factors. The independent variables included in the propensity score model were parental age at the child's birth, maternal smoking and antidepressant use during pregnancy, parental history of affective disorder, and parental history of psychiatric disorder. We then used greedy match algorithms to match the exposed group to the unexposed group. After the matched pairs were identified, differences between matched pairs were evaluated. We then repeated the analysis among the PSM subcohort with additional adjustment for the calendar year of birth, sex of the child, and parity.

The 3-month cutoff point that we defined as the susceptible period was based on the fact that spermatogenesis takes ~70 to 90 days, whereas it may also be possible that SSRIs induce adverse effects (including sperm damage) at the primitive stage. Hence, we defined another exposure period as 6 months before conception and repeated all the above analyses.

RESULTS

Among the 781 470 singletons included in the study, 7216 (0.92%) children were born to fathers who had redeemed a prescription for SSRIs during the last 3 months before conception. During the study period, a total of 12 520 children were diagnosed with ADHD. The median age at diagnosis of ADHD was 8.56 years (interquartile range: 6.76–10.73 years). Characteristics of the study population are shown in Table 1. Compared with the unexposed group, there was a higher proportion of exposed children born in later calendar years. Fathers of exposed children were more likely to be older than 35 years of age and have a history of psychiatric disorders, including affective disorders, before the birth of the child. Mothers of exposed children were characterized as having higher parity and being older at the child's birth, used antidepressants during pregnancy, and have a history of psychiatric disorders before the child's birth.

During 68 877 person-years of follow-up, we identified 129 cases of ADHD in children born to fathers who used SSRIs during the last 3 months before conception (incidence rate: 187 per 100 000 person-years). This incidence rate corresponded to a 52% increased risk of ADHD compared with the unexposed group (Table 2). The adjusted HR (aHR) of ADHD was 1.46 (95% CI: 1.23–1.74) after adjusting for potential confounders in model 1. Additional adjustment for paternal psychiatric history in model 2 attenuated the estimate slightly (aHR = 1.26, 95% CI: 1.06–1.51). When extending the exposure window to 1 year before conception, SSRI use during any exposure period was associated with a higher risk of ADHD in model 1. However, with additional adjustment for paternal psychiatric history, the risk of ADHD was reduced in former users (aHR = 1.35, 95% CI: 1.10–1.66) as well as in current users (aHR = 1.31, 95% CI: 0.95–1.82).

When stratifying by sex, similar results were found in both boys and girls (data not shown). Restriction to children whose mothers neither used SSRIs during pregnancy nor had affective disorders did not change the estimates substantially (data not shown).

In children born to fathers with affective disorder, there was no association between paternal SSRI use and ADHD in children (aHR = 1.04, 95% CI: 0.60–1.80; model 2). In children born to fathers without affective disorder, the patterns of association remained similar to those of the main analyses (Table 3).

In the sibling analysis, we identified 6409 families with more than 1 child and with at least 1 child with paternal SSRI preconception exposure (Table 4). The risk of ADHD in exposed children decreased when compared with their unexposed siblings (aHR = 0.68, 95% CI: 0.41–1.12).

In the PSM subcohort, the exposed children (N = 7216) and unexposed children (N = 7216) were well balanced on baseline characteristics (Supplemental Table 5). The aHR for paternal SSRI use was 1.36 (95% CI: 1.06–1.76) (Supplemental Table 6).

When extending the exposure period to 6 months before conception, patterns of association were essentially unchanged (data not shown).

DISCUSSION

In this large-scale, population-based study, we found that the observed increased risk of ADHD associated with paternal SSRI use before conception could apparently be a result of confounding by paternal psychopathology. Convergent

TABLE 1 Baseline Characteristics of the Study Population

Characteristic	Paternal SSRI Use During the Last 3 mo Before Conception (*N* = 7216)	No Paternal SSRI Use During the Last 3 mo Before Conception (*N* = 774 254)
	N (%)	*N* (%)
Calendar year of birth		
1996–1998	724 (10.0)	184 404 (23.8)
1999–2001	1103 (15.3)	180 749 (23.4)
2002–2004	1787 (24.8)	175 010 (22.6)
2005–2008	3602 (49.9)	234 091 (30.2)
Sex		
Male	3724 (51.6)	397 260 (51.3)
Female	3492 (48.4)	376 994 (48.7)
Birth weight, g		
<2500	298 (4.1)	25 659 (3.3)
2500–3250	1816 (25.2)	181 026 (23.4)
3250–4000	3748 (51.9)	406 864 (52.5)
4000–8000	1312 (18.2)	154 587 (20.0)
Unknown	42 (0.6)	6118 (0.8)
Parity		
1	2818 (39.0)	330 250 (42.6)
2	2568 (35.6)	293 017 (37.9)
≥3	1830 (25.4)	150 987 (19.5)
Preterm birth, <37 wk		
No	6815 (94.4)	737 433 (95.2)
Yes	401 (5.6)	36 821 (4.8)
Apgar score at 5 min		
0–7	90 (1.2)	9487 (1.2)
8–9	465 (6.4)	46 361 (6.0)
10	6585 (91.3)	709 477 (91.6)
Unknown	76 (1.1)	8929 (1.2)
Maternal age at child's birth, y		
≤25	1004 (13.9)	122 827 (15.9)
26–30	2369 (32.8)	288 366 (37.2)
31–35	2493 (34.6)	258 383 (33.4)
>35	1350 (18.7)	104 678 (13.5)
Paternal age at child's birth, y		
≤25	382 (5.3)	58 969 (7.6)
26–30	1499 (20.8)	216 541 (28.0)
31–35	2514 (34.8)	281 323 (36.3)
>35	2821 (39.1)	217 421 (28.1)
Maternal years of education, y		
≤9	1786 (24.7)	155 528 (20.1)
10–14	3116 (43.2)	375 934 (48.5)
>14	2112 (29.3)	233 833 (28.9)
Unknown	202 (2.8)	18 959 (2.5)
Maternal smoking status[a]		
No	4536 (62.9)	555 001 (71.7)
Yes	1457 (20.2)	133 734 (17.3)
Unknown	1223 (16.9)	85 519 (11.0)
Maternal AD use during pregnancy		
No	6802 (94.3)	764 431 (98.8)
Yes	414 (5.7)	9171 (1.2)
Maternal history of affective disorder		
No	6953 (96.4)	765 083 (98.8)
Yes	263 (3.6)	9171 (1.2)
Paternal history of affective disorder		
No	6412 (88.9)	770 595 (99.5)
Yes	804 (11.1)	3659 (0.5)
Maternal history of psychiatric disorder		

evidence of such confounding includes an obvious decline in association after adjustment for paternal psychopathology, the similarly increased ADHD risk observed in former users and current users, and the null association in exposed children with paternal affective disorders. In addition, in exposed children without paternal affective disorders, there was an increased risk associated with paternal SSRI use. Some fathers might receive SSRI treatment from their general practitioners and are therefore not registered with a diagnosis of affective disorders. Therefore, the increased risk associated with prenatal SSRI use was possibly partly confounded by paternal affective disorders diagnosed outside the hospital, for which we were not able to adjust. Besides, other psychiatric diseases related to SSRI use might also contribute to the observed association. This study also performed a sibling analysis, attempting to remove the effects of shared familial genetic or environmental risk factors. The decreased ADHD risk observed in exposed siblings additionally supported that paternal SSRI use could not be a risk factor of childhood ADHD.

Prenatal exposure to SSRIs, which may disrupt serotonergic neurotransmission in the fetal brain, has been proposed as a risk factor for adverse neurodevelopmental outcomes in childhood, including delayed psychomotor development and altered social-emotional and adaptive behavior.[16] Recent investigations have focused on the possible association between maternal SSRI use during pregnancy and the increased risk of autism spectrum disorder or ADHD, with inconclusive findings. To our knowledge, our study is the first in which researchers investigate the link between paternal SSRI use and ADHD risk in children. Similar to the studies previously mentioned, confounding by indication poses the main challenge in this study because the underlying paternal

TABLE 1 Continued

Characteristic	Paternal SSRI Use During the Last 3 mo Before Conception (*N* = 7216)	No Paternal SSRI Use During the Last 3 mo Before Conception (*N* = 774 254)
	N (%)	*N* (%)
No	6507 (90.2)	734 646 (94.9)
Yes	709 (9.8)	39 608 (5.1)
Paternal history of psychiatric disorder		
No	5346 (74.1)	738 581 (95.4)
Yes	1870 (25.9)	35 673 (4.6)

AD, antidepressant drug.
[a] Maternal smoking information was missing among those children born between 2007 and 2008.

mental health disease itself could be a possible risk factor for ADHD.[32] We adopted several analytic strategies to account for such confounding by indication: (1) regression adjustment, (2) negative controls (ie, former-users analyses), (3) stratified analyses according to paternal history of affective disorders, and (4) sibling analyses. The results of these analyses suggested that paternal psychiatric

TABLE 2 Association Between Paternal SSRI Use Before Conception and ADHD in Offspring

Paternal SSRI Use Before Conception	Offspring With ADHD, *n*	Follow-up No. of Person-Years	HR (95% CI)		
			Crude	Model 1[a]	Model 2[b]
No use during the last 3 mo before conception	12 391	8 790 551	Ref	Ref	Ref
Use during the last 3 mo before conception	129	68 877	1.52 (1.28–1.81)	1.46 (1.23–1.74)	1.26 (1.06–1.51)
No use during the last 1 y before conception	12 324	8 758 403	Ref	Ref	Ref
Use only from the last 1 y to the last 3 mo before conception	94	44 166	1.69 (1.38–2.08)	1.56 (1.27–1.92)	1.35 (1.10–1.66)
Use only during the last 3 mo before conception	36	17 468	1.61 (1.16–2.24)	1.48 (1.07–2.06)	1.31 (0.95–1.82)
Use both before and during the last 3 mo before conception	66	39 391	1.37 (1.08–1.75)	1.34 (1.05–1.71)	1.15 (0.90–1.47)

[a] Adjusted for calendar year of birth, sex of child, parity, maternal age, paternal age, maternal years of education, maternal smoking, maternal psychiatric history, and maternal antidepressant drug use during pregnancy.
[b] Model 1 is further adjusted for paternal psychiatric history.

TABLE 3 Association Between Paternal SSRI Use Before Conception and ADHD in Offspring Born to Fathers Diagnosed With Affective Disorder or Not

Paternal SSRI Use Before Conception	Offspring With ADHD, *n*	Follow-up No. of Person-Years	HR (95% CI)		
			Crude	Model 1[a]	Model 2[b]
Fathers with affective disorder					
No use during the last 3 mo before conception	77	35 767	Ref	Ref	Ref
Use during the last 3 mo before conception	15	7258	1.03 (0.59–1.79)	1.04 (0.60–1.80)	1.04 (0.60–1.80)
No use during the last 1 y before conception	70	32 630	Ref	Ref	Ref
Use only from the last 1 y to the last 3 mo before conception	10	4453	1.11 (0.58–2.16)	1.06 (0.54–2.07)	1.06 (0.54–2.07)
Use only during the last 3 mo before conception	4	1286	1.48 (0.54–4.10)	1.39 (0.51–3.75)	1.39 (0.51–3.75)
Use both before and during the last 3 mo before conception	8	4656	0.86 (0.41–1.78)	0.91 (0.43–1.90)	0.91 (0.43–1.90)
Fathers without affective disorder					
No use during the last 3 mo before conception	12 314	8 754 785	Ref	Ref	Ref
Use during the last 3 mo before conception	114	61 619	1.49 (1.24–1.80)	1.45 (1.21–1.75)	1.32 (1.10–1.59)
No use during the last 1 y before conception	12 254	8 725 774	Ref	Ref	Ref
Use only from the last 1 y to the last 3 mo before conception	84	39 713	1.67 (1.35–2.08)	1.56 (1.26–1.94)	1.41 (1.14–1.76)
Use only during the last 3 mo before conception	32	16 182	1.55 (1.10–2.19)	1.44 (1.02–2.03)	1.32 (0.93–1.87)
Use both before and during the last 3 mo before conception	58	34 734	1.36 (1.05–1.76)	1.34 (1.04–1.74)	1.22 (0.94–1.58)

[a] Adjusted for calendar year of birth, sex of the child, parity, maternal age, paternal age, maternal years of education, maternal smoking, maternal psychiatric history, and maternal antidepressant drug use during pregnancy.
[b] Model 1 is further adjusted for paternal psychiatric history.

TABLE 4 Paternal SSRI Use Before Pregnancy and ADHD in Exposed and Unexposed Siblings From 6409 Families

Paternal SSRI Use Before Conception	No. of Offspring	Offspring With ADHD	HR (95% CI)	
			Crude	Model 1[a]
No use during the last 3 mo before conception	3348	76	Ref	Ref
Use during the last 3 mo before conception	3061	39	0.50 (0.33–0.76)	0.68 (0.41–1.12)

[a] Adjusted for sex of the child, parity, maternal age, paternal age, maternal years of education, maternal smoking, and maternal antidepressant drug use during pregnancy.

illness rather than SSRI exposure might be associated with ADHD liability, consistent with previous studies in which researchers observed the link between parental psychiatric disorder and offspring ADHD.[33–35]

Our study has several methodological strengths. The linkage of several nationwide health registries in Denmark enabled us to conduct a large cohort study with virtually complete follow-up. The information on exposure to SSRIs was based on a national registry, which eliminated the risk of recall bias. The information on ADHD diagnosis was obtained independently of exposure measurement, which could mitigate information bias. Furthermore, the availability of fruitful covariates enabled us to adjust for a number of potential confounders, including sociodemographic factors and parental psychiatric history.

Limitations need to be considered when the results of our study are interpreted. Firstly, we were unable to validate actual use of SSRIs by the fathers during the period of interest because we relied on medical records of prescriptions. This may lead to misclassification of exposure because some patients might not take the medication or may take it later. Nevertheless, the misclassification was most likely nondifferential, which was expected to bias the estimates toward the null. Besides, we did not have information on SSRI treatment given at admission. We expect this problem to be minor because most inpatients most likely continue SSRI treatment after discharge. Secondly, we used only the national health care system for case ascertainment. Thus, children who were diagnosed by private psychiatrists or general practitioners or children who remained undiagnosed at the end of the follow-up would be misclassified as not having ADHD. However, the misclassification is not expected to have a major impact because the underestimation of ADHD cases is most likely nondifferential. Thirdly, fathers who used SSRIs might have other risk factors that would be associated with the risk of ADHD in children, and this selection bias would distort the actual causal inference. To minimize this selection bias, we created a PSM subcohort to balance potential baseline characteristics, and the patterns of association did not change remarkably. Fourthly, we had no sufficient data sources to figure out to what extent our findings are specific to ADHD and not the other common co-occurring dimensions of psychopathology. We would consider this issue thoroughly in further study.

CONCLUSIONS

Paternal SSRI use before conception was associated with a mildly increased risk of ADHD in offspring, especially in the former users who took SSRIs before the susceptible exposure period. However, a null association was observed in exposed children with paternal affective disorders, and decreased ADHD risks were observed among exposed siblings, which suggested that paternal underlying indications related to SSRI use or other unmeasured confounding factors may explain the increased risk.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
aHR: adjusted hazard ratio
CI: confidence interval
DMBR: Danish Medical Birth Registry
DPCRR: Danish Psychiatric Central Research Register
HR: hazard ratio
ICD-10: *International Classification of Diseases, 10th Revision*
PSM: propensity score–matched
SSRI: selective serotonin reuptake inhibitor

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