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Attention-deficit hyperactivity disorder in children born to mothers with infertility: a population-based cohort study

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STUDY QUESTION: Is the risk of attention-deficit hyperactivity disorder (ADHD) increased in children born to mothers with infertility, or after receipt of fertility treatment, compared to mothers with unassisted conception?

SUMMARY ANSWER: Infertility itself may be associated with ADHD in the offspring, which is not amplified by the use of fertility treatment.

WHAT IS KNOWN ALREADY: Infertility, and use of fertility treatment, is common. The long-term neurodevelopmental outcome of a child born to a mother with infertility, including the risk of ADHD, remains unclear.

STUDY DESIGN, SIZE, DURATION: This population-based cohort study comprised all singleton and multiple hospital births in Ontario, Canada, 2006–2014. Outcomes were assessed up to June 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Linked administrative datasets were used to capture all hospital births in Ontario, maternal health and pregnancy measures, fertility treatment and child outcomes. Included were all children born at ≥24 weeks gestation between 2006 and 2014, and who were alive at age 4 years. The main exposure was mode of conception, namely (i) unassisted conception (reference group), (ii) infertility without fertility treatment (history of an infertility consultation with a physician within 2 years prior to conception but no fertility treatment), (iii) ovulation induction (OI) or intrauterine insemination (IUI) and (iv) IVF or intracytoplasmic sperm injection (ICSI). The main outcome was a diagnosis of ADHD after age 4 years and assessed up to June 2020. Hazard ratios (HRs) were adjusted for maternal age, income quintile, rurality, immigration status, smoking, obesity, parity, any drug or alcohol use, maternal history of mental illness including ADHD, pre-pregnancy diabetes mellitus or chronic hypertension and infant sex. In addition, we performed pre-planned stratified analyses by mode of delivery (vaginal or caesarean delivery), infant sex, multiplicity (singleton or multiple), timing of birth (term or preterm <37 weeks) and neonatal adverse morbidity (absent or present).

MAIN RESULTS AND THE ROLE OF CHANCE: The study included 925 488 children born to 663 144 mothers, of whom 805 748 (87%) were from an unassisted conception, 94 206 (10.2%) followed infertility but no fertility treatment, 11 777 (1.3%) followed OI/IUI and 13 757 (1.5%) followed IVF/ICSI. Starting at age 4 years, children were followed for a median (interquartile range) of 6 (4–8) years. ADHD occurred among 7.0% of offspring in the unassisted conception group, 7.5% in the infertility without fertility treatment group, 6.8% in the OI/IUI group and 6.3% in the IVF/ICSI group. The incidence rate (per 1000 person-years) of ADHD was 12.0 among children in the unassisted conception group, 12.8 in the infertility without fertility treatment group, 12.9 in the OI/IUI group and 12.2 in the IVF/ICSI

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group. Relative to the unassisted conception group, the adjusted HR for ADHD was 1.19 (95% CI 1.16–1.22) in the infertility without fertility treatment group, 1.09 (95% CI 1.01–1.17) in the OI/IUI group and 1.12 (95% CI 1.04–1.20) in the IVF/ICSI group. In the stratified analyses, these patterns of risk for ADHD were largely preserved. An exception was seen in the sex-stratified analyses, wherein females had lower absolute rates of ADHD but relatively higher HRs compared with that seen among males.

LIMITATIONS, REASONS FOR CAUTION: Some mothers in the isolated infertility group may have received undocumented OI oral therapy, thereby leading to possible misclassification of their exposure status. Parenting behaviour, schooling and paternal mental health measures were not known, leading to potential residual confounding.

WIDER IMPLICATIONS OF THE FINDINGS: Infertility, even without treatment, is a modest risk factor for the development of ADHD in childhood. The reason underlying this finding warrants further study.

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Key words: infertility / attention-deficit hyperactivity disorder / assisted reproductive technology / neurodevelopment / risk factors / epidemiology / child follow-up / pregnancy

Introduction

There is currently limited research examining the long-term neurodevelopmental outcomes of children born to women with infertility and/or fertility treatment. Previous work has demonstrated a higher risk of impaired behavioural, emotional and cognitive development, as well as mental disorders after exposure to fertility treatment (Svahn *et al.*, 2015). However studies supporting a link between fertility treatment and attention-deficit hyperactivity disorder (ADHD) have been inconsistent. There remains uncertainty about whether reported associations stem from the parental infertility aetiology, the fertility treatment or some other confounding factors.

Methodological limitations of previous studies include small sample sizes, limited response rates, single fertility centres and cross-sectional design (Wagenaar *et al.*, 2009; Beydoun *et al.*, 2010; Mains *et al.*, 2010; Halliday *et al.*, 2014). More robust data from population-based studies linking health administrative registries have reported a modest association between maternal receipt of IVF and pharmacologically treated ADHD in the exposed offspring (Källén *et al.*, 2011). Another register-based study reported an increased risk of ADHD in children born after ovulation induction (OI) with or without intrauterine insemination (IUI), but not after IVF (Bay *et al.*, 2013).

The influence of infertility without fertility treatment on risks of ADHD merits further study. For example, among mothers with infertility, their offspring have a reportedly higher risk of ADHD in adulthood (Svahn *et al.*, 2015). However, in a prospective cohort study of children aged 5 years, infertility was not associated with ADHD (Bay *et al.*, 2014). Infertility and fertility treatment are associated with adverse pregnancy outcomes that may predispose to ADHD, including caesarean section, multiple pregnancy and preterm birth (Halmøy *et al.*, 2012; Velez *et al.*, 2014; Curran *et al.*, 2015; Elias *et al.*, 2020; Lodge-Tulloch *et al.*, 2021; Richmond *et al.*, 2022). The role of these adverse pregnancy outcomes on any possible association between infertility, fertility treatment and ADHD also warrants clarification (Hart and Norman, 2013).

There is a current paucity in research with respect to the association between infertility, fertility treatment and offspring ADHD, relative to unassisted conception. This population-based cohort study was undertaken to address this knowledge gap.

Materials and methods

Setting and design

A population-based cohort study was conducted in Ontario, Canada, through linkage of administrative datasets at ICES (www.ices.on.ca) by a trained data analyst. ICES is an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long-Term Care. As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use healthcare data for the purposes of health system analysis, evaluation and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. ICES contains patient-level administrative health records including obstetrical and childhood inpatient and outpatient care received under the publicly-funded Ontario Health Insurance Program (OHIP). Pregnancy characteristics, including conception type, were obtained from the Better Outcomes Registry & Network (BORN) Ontario database and its related Niday Legacy data sets (www.bornontario.ca/en/data/data-dictionary/legacy-datasets/), that capture approximately 99% of hospital births in Ontario and have been previously validated for completeness and accuracy (Ontario, 2019). All linked datasets at ICES and codes used for this study are described in Supplementary Table SI, SII and SIII.

This study included all singleton and multiple hospital livebirths at ≥24 weeks gestation among mothers aged 18–55 years at the time of delivery with a valid OHIP number. Surrogate pregnancies were excluded due to the complexities of biological and gestational factors introduced by this procedure. Excluded were also pregnancies that resulted in induced abortions or child death prior to 4 years of age, or those with missing records (Fig. 1).

Exposure and outcome

The exposure was conception type as recorded in the Ontario Birth Registry ('BORN'), namely: (i) unassisted conception (reference group); (ii) infertility without fertility treatment, defined as history of an infertility consultation with a physician within 2 years prior to conception, as defined by OHIP billing code ICD-9 628 in the absence of fertility treatment; (iii) OI/IUI; and (iv) IVF or intracytoplasmic sperm

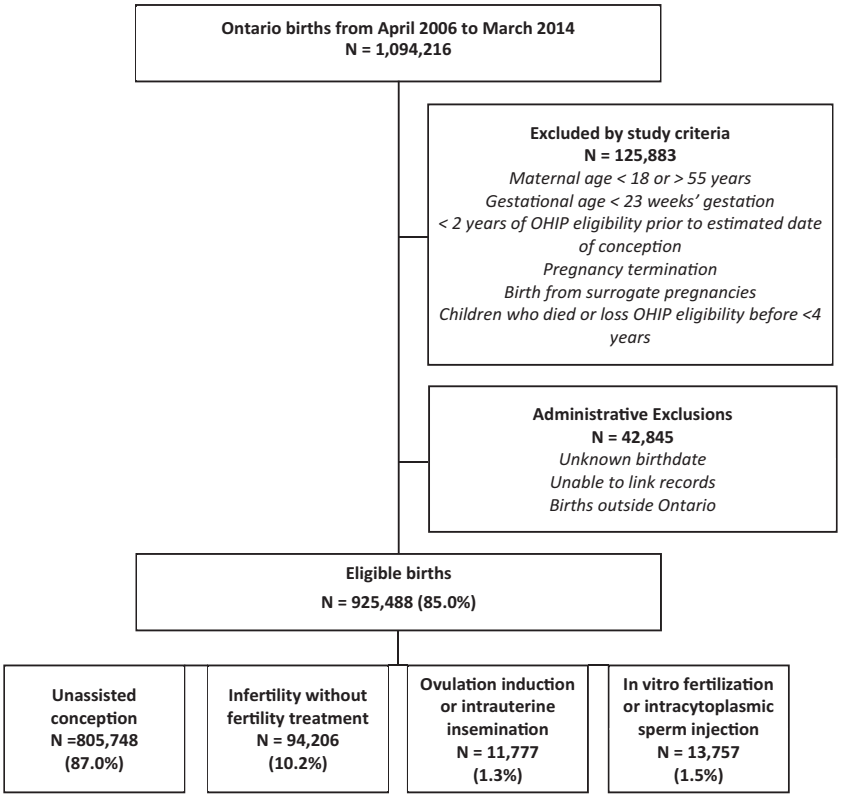

Figure 1. Study flow chart for cohort creation. OHIP, Ontario Health Insurance Program.

injection (ICSI) as in other population-based cohort studies (Declercq *et al.*, 2014).

The outcome of interest was a diagnosis of ADHD in children after 4 years, defined as ≥2 outpatient diagnoses (OHIP billing code ICD-9 312, 313, 314) identified by either a paediatrician or psychiatrist, and/or ≥1 diagnosis during a hospitalization (ICD-10 F90, F91). This algorithm is similar to other register-based cohort studies examining ADHD (Bay *et al.*, 2013; Svahn *et al.*, 2015; Vasiliadis *et al.*, 2017).

Statistical analysis

Time-to-event analyses were conducted using multivariable Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with the child's age as the underlying time scale starting at age 4 years (time zero). A robust sandwich-type estimator was used to account for correlation among multiple livebirths among the same woman. Each child was considered to be exposed to fertility treatment or not exposed to fertility treatment. Censoring was at death, loss of OHIP eligibility or the end of the study period (30 June 2020).

We adjusted, *a priori*, for covariates that might confound the relation between fertility treatment and risk of ADHD, including maternal age, income quintile, rurality, immigration status, smoking, illicit substance use, alcohol use, parity, pre-pregnancy diabetes mellitus or chronic hypertension, obesity, infant sex and history of mental illness defined as the presence of one or more inpatient visits, one or more emergency department visits or two or more outpatient visits with a mental health and addiction (MHA)-related diagnosis (i.e. substance use and addiction disorders, psychotic disorders, mood and anxiety disorders, ADHD) in the mother within 2 years prior to estimated date of conception and up to 19 months postpartum.

Given that several variables were expected to be effect modifiers, we performed pre-planned stratified analyses by mode of delivery (vaginal or caesarean delivery), infant sex at birth (female or male), multiplicity (singleton or multiple), timing of birth (term ≥ 37 weeks or preterm <37 weeks) and neonatal adverse morbidity (absent or present) (Wanigaratne *et al.*, 2016).

We conducted a sensitivity analysis restricted to the infertile population, where the exposure of interest was OI/IUI or IVF/ICSI, each relative to infertility without fertility treatment (reference group). Also, given that fertility treatments may have changed over time, we conducted a sensitivity analysis adding year of birth to the adjusted model. Given that surveillance data now report a diagnosis of ADHD as early as age 2 years (Visser *et al.*, 2015), we conducted sensitivity analysis with follow-up for the outcome starting at age 2 years. In addition, to evaluate the role of BMI as a continuous variable, we conducted a sensitivity analysis in which we adjusted for maternal pre-pregnancy BMI in place of diagnosed obesity, with that analysis limited to births in whom maternal BMI was available. As maternal age may not be linearly related to infertility or ADHD, another sensitivity analysis adjusted for maternal age as a categorical variable (<25, 25–29, 30–34, 35–39, 40–44, ≥45 years), rather than as a continuous variable.

Table I Characteristics of 925 488 livebirths in Ontario, 2006–2014, according to exposure group.

	Unassisted conception (N = 805 748)	Infertility without fertility treatment (N = 94 206)	Ovulation Induction or intrauterine insemination (N = 11 777)	In vitro fertilization or intracytoplasmic sperm injection (N = 13 757)
Maternal demographics				
Mean ± SD maternal age, years	29.9 ± 5.3	33.2 ± 4.7	32.9 ± 4.4	35.5 ± 4.9
Age categories, years				
<25	133 501 (16.6)	3239 (3.4)	292 (2.5)	75 (0.6)
25–29	232 517 (28.9)	17 508 (18.6)	2303 (19.6)	1271 (9.2)
30–34	279 167 (34.6)	36 516 (38.8)	4994 (42.4)	4684 (34.1)
35–39	135 084 (16.8)	28 371 (30.1)	3321 (28.2)	5079 (36.9)
40–44	24 476 (3.0)	8032 (8.5)	836 (7.0)	1994 (14.5)
45+	1003 (0.1)	540 (0.6)	31 (0.3)	654 (4.7)
Income quintile				
1 (lowest)	176 952 (22.0)	14 793 (15.7)	1465 (12.4)	1267 (9.2)
2	161 358 (20.0)	16 655 (17.7)	1958 (16.6)	2164 (15.7)
3	165 982 (20.6)	19 814 (21.0)	2510 (21.3)	2909 (21.2)
4	171 017 (21.2)	23 254 (24.7)	3261 (27.7)	3713 (27.0)
5 (highest)	130 439 (16.2)	19 690 (20.9)	2583 (22.0)	3704 (26.9)
Rural residence	63 968 (7.9)	4067 (4.3)	682 (5.8)	500 (3.6)
Immigrant to Canada	185 191 (23.0)	27 745 (29.5)	2238 (19.0)	3568 (26.0)
Primiparous	328 271 (40.7)	47 579 (50.5)	7492 (63.6)	9544 (69.4)
Maternal comorbidities[a]				
History of polycystic ovary syndrome	4930 (0.6)	3367 (3.6)	706 (6.0)	375 (2.7)
History of endometriosis	2393 (0.3)	1787 (1.9)	248 (2.1)	569 (4.1)
Obesity[b]	73 174 (9.1)	9376 (10.0)	1821 (15.5)	1240 (9.0)
Smoking	83 612 (10.4)	3263 (3.5)	360 (3.1)	207 (1.5)
Substance use[c]	10 601 (1.3)	244 (0.3)	37 (0.3)	34 (0.3)
Alcohol use	1204 (0.2)	51 (0.1)	10 (0.1)	7 (0.1)
Chronic hypertension	19 401 (2.4)	3562 (3.8)	481 (4.1)	540 (3.9)
Pre-pregnancy diabetes mellitus	12 134 (1.5)	2727 (2.9)	389 i3.3)	350 (2.5)
History of mental illness[d]	211 269 (26.2)	25 460 (27.0)	3002 (25.5)	3386 (24.6)
Pregnancy outcomes				
Placenta previa	4509 (0.6)	923 (1.0)	137 (1.2)	354 (2.6)
Placental abruption	3549 (0.4)	530 (0.6)	78 (0.7)	136 (1.0)
Gestational diabetes	34 028 (4.2)	7173 (7.6)	1111 (9.4)	1209 (8.8)
Gestational hypertension	36 614 (4.5)	5428 (5.8)	1054 (9.0)	1320 (9.6)
Multiple pregnancy	18 886 (2.3)	6144 (6.5)	2503 (21.3)	5531 (40.2)
Median (IQR), gestational age at birth	39 (38–40)	39 (38–40)	38 (37–40)	38 (36–39)
<28 weeks	1717 (0.2)	492 (0.5)	119 (1.0)	191 (1.4)
28–34 weeks	11 164 (1.4)	2437 (2.6)	636 (5.4)	1121 (8.2)
34–36 weeks	102 025 (12.7)	16 223 (17.2)	2840 (24.1)	5052 (36.7)
≥37 weeks	690 842 (85.7)	75 054 (79.7)	8182 (69.5)	7393 (53.7)
Caesarean delivery	219 310 (27.2)	35 287 (37.5)	4957 (42.1)	7605 (55.3)
Labour Induction	194 900 (24.2)	23 981 (25.5)	3486 (29.6)	3872 (28.2)
Infant sex				
Female	392 440 (48.7)	46 018 (48.9)	5769 (49.0)	6770 (49.2)
Male	413 308 (51.3)	48 188 (51.2)	6008 (51.0)	6987 (50.8)

All data are presented as a number (%) unless specified otherwise. ADHD, attention-deficit hyperactivity disorder; IQR, interquartile range; OHIP, Ontario Health Insurance Program.
[a]Based upon hospitalizations, emergency room visits or outpatient physician visits from within 2 years before conception, up to 19 weeks gestation.
[b]Obesity is defined as a pre-pregnancy body mass index ≥30 kg/m^2, if recorded in Better Outcomes Registry and Network, or an OHIP billing code (dxcode = 278) for obesity in 2-year lookback prior to estimated date of conception.
[c]Substance use is defined as any marijuana, cocaine, gas/glue, hallucinogens, methadone, narcotics, opioids and other substance use.
[d]Maternal mental illness is defined as the presence of 1 or more inpatient visits, 1 or more emergency department visits, or 2 or more outpatient visits with a mental health and addiction-related diagnosis (i.e. substance use and addiction disorders, psychotic disorders, mood and anxiety disorders, maternal ADHD) within 2 years prior to estimated date of conception and up to 19 months of age for infant.

Table II Risk of ADHD, starting at age 4 years, by type of conception.

Conception type	No. with ADHD/ no. at risk	Rate of ADHD per 1000 person-years	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
Unassisted conception	56 479/805 748	12.0	1.00 (ref)	1.00 (ref)
Infertility without fertility treatment	7047/94 206	12.8	1.07 (1.04–1.10)	1.19 (1.16–1.22)
Ovulation induction or intrauterine insemination	802/11 777	12.9	1.05 (0.98–1.13)	1.09 (1.01–1.17)
In vitro fertilization or intracytoplasmic sperm injection	861/13 757	12.2	0.98 (0.91–1.05)	1.12 (1.04–1.20)

[a]Adjusted for maternal age, income quintile, rurality, immigration status, smoking, obesity, parity, any drug or alcohol use, maternal history of mental illness (including maternal ADHD), pre-pregnancy diabetes mellitus or chronic hypertension and infant sex.

The proportional hazards assumption was examined by introducing interaction terms for time and covariates in the Cox model. All statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc.).

Ethical approval

This study was approved by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board.

Results

Of the 1 094 216 livebirths in Ontario from April 2006 to March 2014, 925 488 children born to 663 144 mothers were included in the study following exclusions: 805 748 (87.0%) births from an unassisted conception, 94 206 (10.2%) following infertility but no infertility treatment, 11 777 (1.3%) following OI/IUI and 13 757 (1.5%) following IVF/ICSI (Fig. 1).

Differences in baseline demographics were observed according to the mode of conception (Table I). A greater proportion of mothers with unassisted conception were younger than 35 years at time of conception, multiparous and consumed tobacco as compared to all other groups. Mothers who used OI/IUI had a higher proportion of diagnosed obesity, chronic hypertension and diabetes mellitus compared to all other groups. Those with infertility without fertility treatment or who used OI/IUI or IVF/ICSI were more likely to deliver by caesarean section as compared to mothers with unassisted conception. Pregnancies following OI/IUI and IVF/ICSI were more likely to result in multiple pregnancy. Overall, there was a relatively equal distribution of male and female births by conception type.

We identified 65 189 children with a diagnosis of ADHD with a mean age at diagnosis of 6.4 years (SD 2.0). There were 56 479 (7.0%) children with ADHD born to mothers with unassisted conception (mean age at diagnosis 6.4 years, SD 2.0), 7047 (7.5%) with ADHD born to mothers with infertility without fertility treatment (mean age at diagnosis 6.3 years, SD 2.0), 802 (6.8%) with ADHD born to mothers treated with OI/IUI (mean age at diagnosis 6.1 years, SD 2.0) and 861 (6.3%) with ADHD born to a mother treated with IVF/ICSI (mean age at diagnosis 6.0 years, SD 2.0).

The incidence rate of ADHD (per 1000 person-years) was 12.0 among children in the unassisted conception group, 12.8 in the infertility without fertility treatment group, 12.9 in the OI/IUI group and 12.2 in the IVF/ICSI group (Table II). The unadjusted HR of ADHD was higher in children born to women with infertility without fertility treatment (HR 1.07, 95% CI 1.04–1.10) (Table II), which retained significance after adjustment (HR 1.19, 95% CI 1.16–1.22). Both, OI/IUI (HR 1.09, 95% CI 1.01–1.17) and IVF/ICSI (HR 1.12, 95% CI 1.04–1.20) (Table II) conferred similar and slightly elevated HRs of ADHD in the adjusted models, despite lower incidence rates of the disorder.

The aforementioned patterns of risk for ADHD were largely preserved across strata (Table III). An exception was seen in the sex-stratified analyses, wherein females had lower overall incidence rates of ADHD, but relatively higher HRs following infertility or fertility treatment than seen among males (Table III). Of note, in these stratified analyses, male infants, those born preterm and those with neonatal adverse morbidity had the highest overall incidence rates of ADHD (Supplementary Table SIII).

In a sensitivity analysis restricted to the infertile population, relative to the infertility without fertility treatment group, the adjusted HR was 0.92 (95% CI 0.85–0.99) for children born after OI/IUI and 0.87 (95% CI 0.81–0.94) for those born after IVF/ICSI (Supplementary Table SIV). The sensitivity analysis adding year of birth to the adjusted model resulted in similar results to the main analysis (Supplementary Table SV). In the sensitivity analysis assessing for ADHD starting at age 2 years, the HRs were similar to those seen when ADHD was analysed from age 4 years (Supplementary Table SVI). In the sensitivity analyses limited to 293 123 children in whom maternal BMI was available (Supplementary Table SVII), or when considering age as a categorical variable in the adjusted model (Supplementary Table SVIII), the results were similar in magnitude and direction, although not always statistically significant.

Discussion

In this population-based cohort study of all hospital livebirths in Ontario, 2006–2014, we found a higher risk of ADHD diagnosed in children born to a mother with infertility without fertility treatment, which was not amplified by the use of fertility treatment. In all exposure categories, females had lower incidence rates of ADHD than their male counterparts, but relatively more pronounced HRs.

In a study of severe ADHD in adulthood, an increased risk of ADHD was reported in the offspring of mothers with infertility; however, that study did not distinguish between being diagnosed with infertility versus receiving fertility treatment (Svahn *et al.*, 2015). Another

Table III Risk of ADHD, starting at age 4 years, by type of conception, stratified by pregnancy characteristics.

Stratification variable	No. with ADHD/ no. at risk	Rate of ADHD per 1000 person-years	Adjusted hazard ratio (95% CI)[a]
Mode of delivery			
Vaginal birth			
Unassisted conception	40 084/586 340	11.7	1.00 (reference)
Infertility without fertility treatment	4181/58 900	12.2	1.19 (1.15–1.23)
Ovulation induction or intrauterine insemination	428/6819	12.0	1.07 (0.97–1.18)
In vitro fertilization or intracytoplasmic sperm injection	353/6152	11.3	1.06 (0.95–1.19)
Caesarean birth			
Unassisted conception	16/389/219 310	12.7	1.00 (reference)
Infertility without fertility treatment	2865/35 287	13.7	1.17 (1.12–1.22)
Ovulation induction or intrauterine insemination	374/4957	14.2	1.08 (0.97–1.21)
In vitro fertilization or intracytoplasmic sperm injection	508/7605	13.0	1.10 (0.99–1.21)
Infant sex			
Female			
Unassisted conception	16 901/392 440	7.2	1.00 (reference)
Infertility without fertility treatment	2270/46 018	8.3	1.28 (1.22–1.34)
Ovulation induction or intrauterine insemination	273/5769	8.9	1.24 (1.10–1.40)
In vitro fertilization or intracytoplasmic sperm injection	295/6770	8.4	1.29 (1.14–1.46)
Male			
Unassisted conception	39 578/413 308	16.6	1.00 (reference)
Infertility without fertility treatment	4777/48 188	17.2	1.15 (1.12–1.19)
Ovulation induction or intrauterine insemination	529/6008	16.9	1.03 (0.94–1.12)
In vitro fertilization or intracytoplasmic sperm injection	566/6987	16.0	1.05 (0.96–1.14)
Multiplicity			
Singleton			
Unassisted conception	55 141/786 862	11.9	1.00 (reference)
Infertility without fertility treatment	6571/88 062	12.8	1.19 (1.16–1.23)
Ovulation induction or intrauterine insemination	630/9274	13.0	1.10 (1.01–1.19)
In vitro fertilization or intracytoplasmic sperm injection	527/8226	12.8	1.17 (1.07–1.28)
Multiple			
Unassisted conception	1338/18 886	12.2	1.00 (ref)
Infertility without fertility treatment	476/6144	12.3	1.12 (0.98–1.28)
Ovulation induction or intrauterine insemination	172/2503	12.9	1.05 (0.87–1.26)
In vitro fertilization or intracytoplasmic sperm injection	334/5531	11.4	1.00 (0.86–1.17)
Timing of birth			
Term birth ≥37 weeks' gestation			
Unassisted conception	51 425/749 116	11.7	1.00 (ref)
Infertility without fertility treatment	6079/83 692	12.4	1.19 (1.15–1.22)
Ovulation induction or intrauterine insemination	621/9557	12.3	1.07 (0.99–1.16)
In vitro fertilization or intracytoplasmic sperm injection	589/9764	11.9	1.11 (1.02–1.21)
Preterm birth <37 weeks' gestation			
Unassisted conception	5054/56 632	15.3	1.00 (ref)
Infertility without fertility treatment	968/10 514	15.4	1.16 (1.07–1.25)
Ovulation induction or intrauterine insemination	181/2220	15.5	1.05 (0.89–1.23)
In vitro fertilization or intracytoplasmic sperm injection	272/3993	13.1	0.99 (0.86–1.14)

(continued)

Table III Continued

Stratification variable	No. with ADHD/ no. at risk	Rate of ADHD per 1000 person-years	Adjusted hazard ratio (95% CI)[a]
Neonatal adverse morbidity			
None			
Unassisted conception	52 707/765 135	11.7	1.00 (ref)
Infertility without fertility treatment	6379/87 462	12.4	1.19 (1.15–1.22)
Ovulation induction or intrauterine insemination	677/10 378	12.3	1.07 (0.99–1.16)
In vitro fertilization or intracytoplasmic sperm injection	694/11 647	11.6	1.09 (1.01–1.18)
Present			
Unassisted conception	3772/40 613	16.8	1.00 (ref)
Infertility without fertility treatment	668/6744	17.6	1.18 (1.08–1.29)
Ovulation induction or intrauterine insemination	125/1399	17.7	1.11 (0.91–1.34)
In vitro fertilization or intracytoplasmic sperm injection	167/2110	15.7	1.08 (0.91–1.28)

ADHD, attention-deficit hyperactivity disorder.
[a]Adjusted for maternal age, income quintile, rurality, immigration status, smoking, obesity, parity, any drug or alcohol use, maternal history of mental illness (including ADHD), pre-pregnancy diabetes mellitus or chronic hypertension and infant sex. When a variable is stratified upon, it is not included in the adjusted model.

group found no association between infertility and ADHD in 5-year olds in 1782 children sampled from the Danish National Birth Cohort and using neurodevelopmental assessment tests (Bay *et al.*, 2014).

In our study, children exposed to IVF/ICSI had the lowest rates of diagnosed ADHD compared with other conception groups, but slightly higher adjusted HRs for ADHD. The literature has reported mixed findings on these associations. A nationwide register-based study in Denmark found a small increase in the incidence of mental disorders, including ADHD, in children born after OI/IUI (Bay *et al.*, 2013). In the case of IVF, a large cohort study in Sweden found an association between IVF and increased risk of drug-treated ADHD in children (Källén *et al.*, 2011). In the latter study, the association was attenuated after adjusting for the length of involuntary childlessness, which suggests that the underlying infertility could have been a contributor to the initial association. Similarly, a population-based cohort study in Finland reported that children conceived with fertility treatment had a higher risk of a composite of psychiatric diagnoses (including attention-deficit disorder, ADHD and tic disorder), compared to children conceived without assistance (Rissanen *et al.*, 2020). A high rate of ADHD (27%) was reported in children born after IVF in a survey-based cross-sectional analysis; however, the small sample size, self-reported information and low response rate limit the interpretation of these findings (Beydoun *et al.*, 2010). A registry-based study in Denmark found no association between IVF/ICSI and ADHD (Bay *et al.*, 2013).

Increasing evidence supports that infertility, independent of fertility treatment, confers an increased risk of adverse perinatal outcomes, such as preterm birth, low birthweight, small for gestational age babies and caesarean section (Messerlian *et al.*, 2013; Richmond *et al.*, 2022). In the stratified analysis, the associations between infertility without fertility treatment use and childhood ADHD remained mostly significant in all strata, such as vaginal delivery or caesarean section, singleton pregnancy, term or preterm birth and those with or without adverse neonatal outcomes. This suggests that long-term neurodevelopmental outcomes in children are related to factors of infertility that cannot be explained by perinatal outcomes alone. Reproductive disorders are associated with inflammatory, endocrine and metabolic mechanisms that impede fertility (Vannuccini *et al.*, 2016). Multiple theories have been suggested to explain the development of ADHD due to parental infertility. For example, male and female infertility may be more likely to generate gametes with epigenetic modifications or instability (Paoloni-Giacobino and Chaillet, 2004; Dada *et al.*, 2012). Prenatal androgen exposure due to polycystic ovary syndrome (PCOS) has also been found to increase the risk of childhood ADHD (Berni *et al.*, 2018), as well as maternal obesity and diabetes (Kong *et al.*, 2018). In our study, the prevalence of a PCOS diagnosis was lower (0.6%) in unassisted conceptions than in mothers with infertility without fertility treatment (3.6%), OI/IUI (6.0%) and IVF/ICSI (2.7%).

Female children experienced a slightly higher risk of ADHD following exposure to fertility treatment, though this was not seen in males. This finding has been noted by others (Källén *et al.*, 2011). A higher risk of ADHD in females after fertility treatment could be a consequence of survivor bias; that is, male infants born extremely preterm had greater mortality risk than females (Binet et al., 2012), knowing that fertility treatment is associated with an increased risk of preterm birth (Elias *et al.*, 2020). Even so, fertility treatment has not been consistently found to be a risk factor for ADHD in girls to a greater degree than in boys (Bay *et al.*, 2013). Certainly, further studies are needed to elucidate the role of child sex on ADHD after fertility treatment.

A strength of our study is the use of comprehensive and validated datasets that are representative of >99% of livebirths in Ontario. In addition, we accounted for many confounding factors that have been demonstrated to be important in the aetiology of ADHD development. We had a long follow-up period, which is important in the context of neurodevelopmental disorders such as ADHD, which are often not diagnosed until later in childhood. Limitations include the potential

for misclassification of exposure; some individuals in the infertility group may have used OI medication but were not captured as OI/IUI. There is also the potential for residual confounding, due to unavailability of some data in administrative datasets, such as maternal stress, marital discord, history of breastfeeding, cohabitation and other socio-cultural factors (Källén *et al.*, 2011). Furthermore, we lacked information on genetic factors that have been theorized to play a role in ADHD development (Sciberras *et al.*, 2017). Finally, our study lacks information about paternal age, co-morbidities and behavioural factors that could also contribute to infertility and offspring ADHD. In particular, large cohort studies have demonstrated that both advanced (i.e. >45 years of age) (D'Onofrio *et al.*, 2014) and young (i.e. <20 years of age) (McGrath *et al.*, 2014; Chudal *et al.*, 2015) paternal age are associated with increased risks of ADHD in offspring, with a higher risk when both parents are of young age (Hvolgaard Mikkelsen *et al.*, 2017).

In conclusion, our study suggests a modest association between infertility itself and risk of childhood ADHD that was not amplified with the use of fertility treatment. Further research is needed to identify factors associated with parental infertility that could contribute to offspring ADHD.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data set from this study is held securely in coded form at ICES. While data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programmes may rely upon coding templates or macros.

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Authors' roles

A.F. and M.P.V. interpreted the analyses and wrote the first draft of the manuscript. N.D., D.B.F., S.N.V., J.G.R. and M.P.V. conceived the study, obtained access to the data, interpreted the analyses and revised the manuscript for important intellectual content. J.P. contributed to study design, interpretation of results and revised the manuscript for important intellectual content. M.D. performed the analyses and contributed to writing of the manuscript.

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Conflict of interest

None of the authors report conflicts of interest relevant to this study.

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