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ORIGINAL ARTICLE ***Reproductive epidemiology***

Maternal spontaneous abortion and the risk of attention-deficit/hyperactivity disorder in offspring: a population-based cohort study

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STUDY QUESTION: Is a maternal history of spontaneous abortion (SA) associated with an increased risk of attention-deficit/hyperactivity disorder (ADHD) in offspring?

SUMMARY ANSWER: Our results suggest an association between maternal history of SA and ADHD in offspring, with the risk increasing with the number of maternal SA and highest in the firstborn children whose mothers had had recurrent SAs after adjusting for a number of potential confounders.

WHAT IS KNOWN ALREADY: A history of SA has been associated with more complications in next pregnancies and adverse childbirth outcomes, which are risk factors for ADHD in the offspring. However, no previous study has investigated whether maternal SA increases risk of ADHD in the offspring.

STUDY DESIGN, SIZE, DURATION: This population-based study included all live-born children in Denmark from 1 January 1995 to 31 December 2012 ($n = 1\,062\,667$). All children were followed from 3 years of age until the day of ADHD diagnosis, death, emigration or 31 December 2016, whichever came first.

PARTICIPANTS/MATERIALS, SETTING, METHODS: There were 130 206 (12.2%) children born to mothers who had at least one SA. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

MAIN RESULTS AND THE ROLE OF CHANCE: During a median follow-up of 9.4 years (interquartile range, 5.4–14.3), 25 747 children were diagnosed with ADHD. Overall, children of mothers with a history of SA had an increased rate of ADHD (HR, 1.11; 95% CI, 1.07 to 1.15). The HRs increased with the number of maternal SA, 1.09 (95% CI, 1.05 to 1.13) for one SA and 1.22 (95% CI, 1.12 to 1.33) for at least two SAs, respectively. These findings were consistent when we took into consideration a number of factors, such as maternal socioeconomic status, type of SA, birth order, parental history of psychiatric disorders, pregnancy characteristics and adverse birth outcomes.

LIMITATIONS, REASONS FOR CAUTION: Misclassification of SA was possible as we used population-based register data to capture maternal history of SA. However, any misclassification of maternal history of SA would be non-differential with regard to the diagnosis of ADHD in offspring, which generally leads to underestimation of the associations. Furthermore, probabilistic sensitivity analysis suggested that only 1% of change in the estimate may have been due to misclassification of SA.

WIDER IMPLICATIONS OF THE FINDINGS: SA is quite frequent (varying from 15 to 20%), and a small increase of neurodevelopmental problems in offspring could have major public health implications.

[†]These two authors contributed equally to the manuscript and considered as co-first authors.

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Key words: spontaneous abortion / attention-deficit/hyperactivity disorder / cohort study / epidemiology / association

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders (Visser *et al.*, 2014). ADHD often emerges during childhood and persists into adulthood (Mannuzza *et al.*, 2003), with prevalence ranging from 3 to 7% globally (Sayal *et al.*, 2018) and even up to 10% reported in recent studies (Visser *et al.*, 2014; Thomas *et al.*, 2015). Given the fact that ADHD can have negative impacts on patients and their families and even society at large, identification of ADHD risk factors has major public health significance (Galéra *et al.*, 2011; Shaw *et al.*, 2012).

The aetiology of ADHD is complex and remains mostly unknown (Faraone *et al.*, 2005; Millichap, 2008). An increasing body of evidence has suggested a role of foetal programming on ADHD development (Sciberras *et al.*, 2017). Prenatal exposure to adverse intrauterine environment could lead to an increased susceptibility to neurodevelopmental disorders later in life (Bale *et al.*, 2010). Maternal fertility problems may be linked to factors that also influence offspring's neurodevelopment and ADHD risk (Bay *et al.*, 2013; Svahn *et al.*, 2015). Spontaneous abortion (SA) is one of the common adverse pregnancy outcomes, affecting ~20% of pregnant women with recurrent rates of 1 to 2% (Sedgh *et al.*, 2016). Women with a history of SA are more likely to have pregnancy complications, such as gestational diabetes (Bhattacharya *et al.*, 2008), impaired placentation (Gunnarsdottir *et al.*, 2014) and heightened oxidative stress (Jauniaux *et al.*, 2006), which may predispose children to developing ADHD (Getahun *et al.*, 2013). Women with SA often give birth to children with more adverse birth outcomes, such as preterm birth, low birth weight, congenital anomalies and lower Apgar score (Brown *et al.*, 2008), which have been demonstrated to be risk factors for ADHD (Li *et al.*, 2011; Sucksdorff *et al.*, 2015). For example, a population-based study in Norway reported a 1.3- and 5-fold risk for ADHD in individuals born preterm (<37 gestational weeks) and extremely preterm (<28 gestational weeks), respectively (Rommel *et al.*, 2017). Furthermore, the risk of those adverse birth outcomes is increased with the number of previous SA (Brown *et al.*, 2008; Ahrens *et al.*, 2016). One study has further shown an association between maternal history of SA and epilepsy (Schupf and Ottman, 2001). However, it is not known whether maternal history of SA increases the risk of ADHD in the offspring. Previous studies have also shown a bidirectional association between SA and psychiatric disorders in women (Fergusson *et al.*, 2008; Toffol *et al.*, 2013), suggesting a role of shared genetic susceptibility and family environment (Fergusson *et al.*, 2008; Toffol *et al.*, 2013).

We hypothesized that maternal SA may lead to an increased risk of ADHD in offspring and the magnitude of risk might differ by the number of maternal SA. Previous studies have suggested that birth order may also signify different levels of hormone exposure *in utero* (Bernstein *et al.*, 1986; Von Behren *et al.*, 2011) that may affect the risk of ADHD in the offspring (Carballo *et al.*, 2013). In this large nationwide cohort study of >1 million persons with a long follow-up in Denmark, we aimed to investigate the association between maternal history of SA and ADHD in offspring, taking into consideration a number of maternal and offspring characteristics, such as sociodemographic factors, pregnancy complications, birth order and adverse birth outcomes (Bhattacharya *et al.*, 2008; Brown *et al.*, 2008; Li *et al.*, 2011; Von Behren *et al.*, 2011; Toffol *et al.*, 2013; Sucksdorff *et al.*, 2015; Rommel *et al.*, 2017).

Materials and Methods

Design and population

We carried out a nationwide cohort study using data from the Danish national registers (a detailed description of registers is provided in Supplementary Table SI) (Timmermans, 2010; Lynge *et al.*, 2011; Mors *et al.*, 2011; Wallach Kildemoes *et al.*, 2011; Schmidt *et al.*, 2015). In Denmark, all live births have a unique personal identification number that permits the accurate linkage of individual-level data. We identified all singleton live births from 1 January 1995 to 31 December 2012 ($n = 1\,129\,030$) from the Danish Medical Birth Registry. We excluded 24 146 children who had missing or extreme gestational age (<154 or >315 days), 4660 stillbirths, 3121 children with chromosomal abnormalities (*International Classification of Disease* [ICD]-10 codes Q90–99) identified from the Danish National Patient Register (DNPR), 523 children without links to their fathers and 14 523 children who died or emigrated within the first 3 years. We further excluded 18 548 children whose mothers were born earlier than 1 January 1960 and did not have valid information on SA (Lynge *et al.*, 2011; Schmidt *et al.*, 2015). We also excluded 842 children whose mothers had a recorded date of abortion during the gestational period of a successful pregnancy. In the final analyses, we included a total of 1 062 667 children (as shown in Fig. 1). We followed each child from 3 years of age until the date of the first diagnosis of ADHD, emigration, death or end of follow-up (31 December 2016), whichever came first. The study was approved by the Danish Data Protection Agency (2015-57-0002).

Data on maternal history of spontaneous abortion

Information on maternal SA was obtained from the DNPR, using ICD codes (ICD-8 codes during 1977–1993: 6438, 6439, 6346 and 6451;

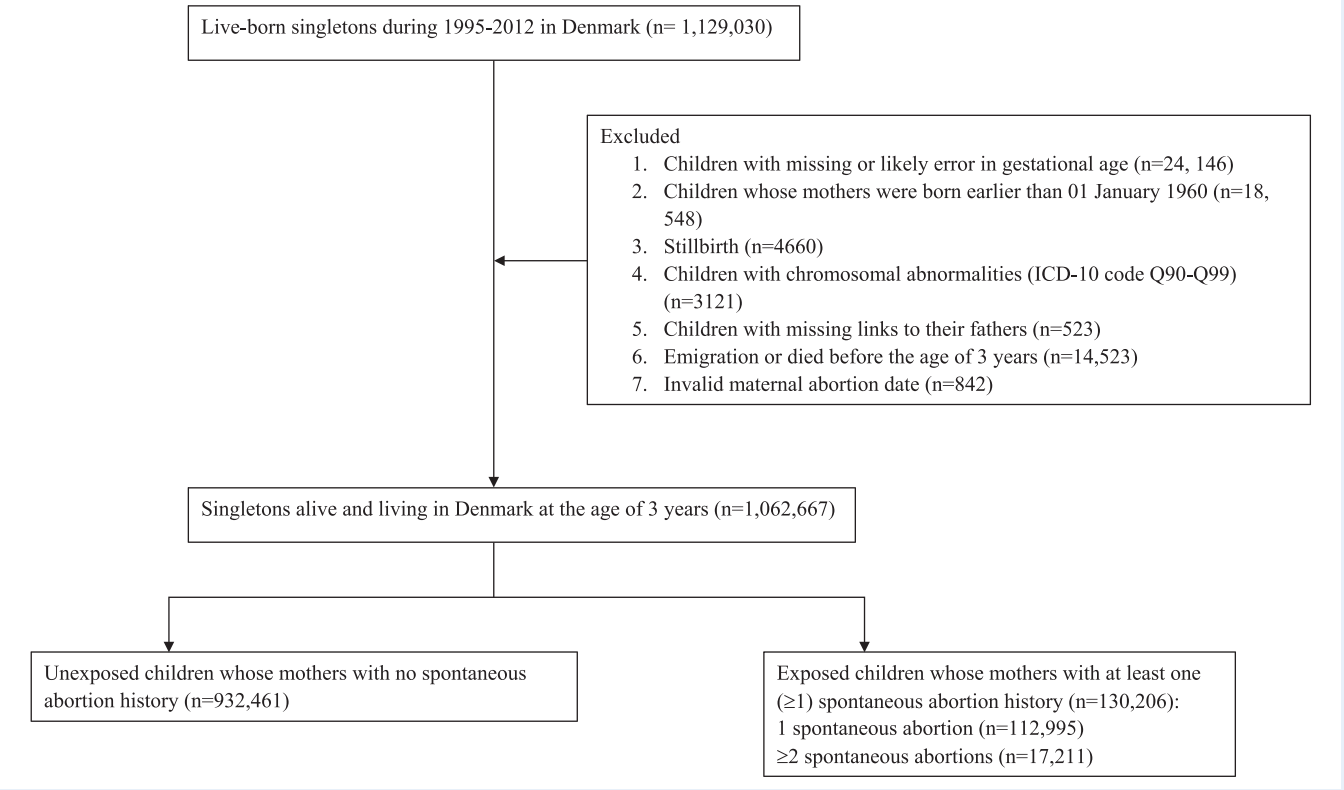

Figure 1 Flowchart showing the identification of the eligible participants and analysis sample.

ICD-10 codes since 1994: O03 and O021) (Lohse *et al.*, 2010). We categorized the children into three groups: (i) unexposed children, (ii) children of mothers who had one single SA (1 SA) before the childbirth and (iii) children of mothers who had at least two SAs (≥2 SAs) before the childbirth.

Identification of ADHD individuals

Children were classified as ADHD individuals if they either had a hospital diagnosis of ADHD or redeemed ADHD medication prescription for at least twice after the age of 3 years. Information on hospital ADHD diagnosis was obtained from the DNPR based on ICD-10 codes (F90.0-F98.8) (Schmidt *et al.*, 2015). Data on ADHD specific drug use were extracted from the National Prescription Register. The Anatomical Therapeutic Chemical codes for ADHD-specific medication were N06BA04 (methylphenidate) and N06BA09 (atomoxetine). Children who had redeemed N06BA07 (modafinil) were included as ADHD individuals only if they had previously redeemed a prescription for either N06BA04 or N06BA07 (Wallach Kildemoes *et al.*, 2011; Pottegård *et al.*, 2012). Two or more medications prescribed on the same date were counted as one prescription. The date of the first ADHD diagnosis or medication was defined as the onset of ADHD. Previous studies have suggested a high validity of using both the hospital register and the prescription register to identify ADHD in children (Christensen *et al.*, 2019; Sun *et al.*, 2019), and the probability of misclassification of ADHD was relatively low and the inter-rater agreement was high (96%) (Mohr-Jensen *et al.*, 2016).

Ethical approval

The study was approved by the Danish Data Protection Agency (No. 2013-41-2569). According to Danish legislation, no informed consent is required for a registry-based study using anonymized data.

Covariates

Based on previous research (Klemetti *et al.*, 2012; Ahrens *et al.*, 2016), the following factors were considered as potential confounders: sex of the child (male, female), preterm birth (yes [gestational age at birth <37 weeks], no), low birth weight (yes [birth weight < 2500 g], no), low Apgar score at 5 min (yes [Apgar score < 7], no), small for gestational age (SGA) (yes [birth weight below the 10th percentile for infants of the same gestational age and sex], no), calendar period of birth (1995–1998, 1999–2002, 2003–2006, 2007–2009, 2010–2012), maternal age at birth (≤25, 26–30, 31–35, ≥36), paternal age at birth (≤25, 26–30, 31–35, ≥36), maternal smoking during pregnancy (yes, no), maternal country of origin (Denmark, other countries), maternal education level (0–9, 10–14, ≥15), maternal cohabitation status (yes, no), maternal history of diabetes (yes, no), maternal hypothyroidism (yes, no), maternal psychiatric disorder before the childbirth (yes, no) and paternal psychiatric disorder before the childbirth (yes, no). The information for maternal social status and origin of country was obtained from the Danish Integrated Database for Longitudinal Labor Market Research (Timmermans, 2010). Information for maternal diabetes, hypothyroidism and parental psychiatric disorders was retrieved from the

DNPR and Danish Psychiatric Central Research Register (Lynge et al., 2011; Mors et al., 2011).

Statistical analyses

We used Cox proportional hazards regression model to estimate the hazard ratio (HR) with 95% confidence intervals (CIs) for the association of maternal history of SA with the risk of ADHD in offspring. The primary analysis was to compare the rate of ADHD in unexposed children with the rates in children of mothers with one SA or with at least two SAs before the childbirth. To control for the correlations of sequential births of the same mother, the robust sandwich estimator for correction of standard errors was used. We investigated the interaction between maternal history of SA and birth order based on the statistical significance of interaction terms in the Cox proportional hazards model. As an increased number of SA may indicate more severe conditions; we thus tested for a trend between maternal history of SAs and ADHD risk in offspring. This assumed an equidistant stepwise function for the level of maternal history of SA (continuous variable coded: no SA = 0, 1 SA = 1, ≥2 SAs = 2). Additionally, we tested whether the associations varied according to sex of the child. We performed four models for adjusting potential confounders. Only sex and birth year were included in Model 1. Model 2 was additionally adjusted for parental age at birth, parity, maternal education level, maternal origin, maternal cohabitation and maternal smoking during pregnancy (Galéra et al., 2011; Hvolgaard Mikkelsen et al., 2016). Model 3 was further adjusted for parental psychiatric disorders before the childbirth, maternal diabetes and hypothyroidism status (Päkkilä et al., 2014; Xiang et al., 2018). In Model 4 we additionally adjusted for preterm birth, low birth weight, low Apgar score at 5 min and SGA.

The positive predictive value of SA is high (97.4%) in the National Patient Register, while sensitivity and specificity have not been reported (Lohse et al., 2010). We tried to account for misclassification of maternal SA by using the probabilistic sensitivity analysis (Kristensen and Irgens, 2000; Orsini et al., 2008). Probabilistic sensitivity analysis was used to provide an external adjustment of the observed odds ratio (OR) upon specification of hypothetical values for maternal SA (Orsini et al., 2008). The probabilistic sensitivity analysis through Monte Carlo simulations involved two iterated steps: (i) draw a random sample from the specified probability density functions of maternal SA and (ii) back-calculate the bias-adjusted OR from maternal SA, which were repeated several times to obtain a bias-adjusted OR (Fox et al., 2005).

We performed mediation analyses to examine whether adverse birth outcomes (low birth weight, preterm birth, low Apgar score and SGA) mediated the association between maternal SA and ADHD in offspring by calculating direct and indirect effects (via the mediator) in the Stata module PARAMED (Emsley and Liu, 2013). The proportion of mediation was calculated as log (natural indirect relationship)/log (total relationship).

We estimated the population attributable fraction by using the adjusted hazard ratio of ADHD in the group whose mothers had a history of SA versus the unexposed group and the prevalence of SA before the childbirth in the entire population (P_{pop}) according to the formula population attributable fraction $= P_{pop} \times (HR-1)/(P_{pop} \times (HR-1)+1)$ (Rockhill et al., 1998). To evaluate the robustness of the results to potential unmeasured confounding, we calculated the *E*-value for the overall estimate using the publicly available online *E*-value calculator for hazard ratios with an outcome prevalence of <15% (https://www.hsph.harvard.edu/tyler-vanderweele/tools-and-tutorials/). The *E*-value is a measure that represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain the association (VanderWeele and Ding, 2017).

Sensitivity analyses

To test the robustness of our results, we did several sensitivity analyses. First, to remove the effect of induced abortion, we repeated our analyses by excluding the mothers who had induced abortion before the childbirth (n = 19 976). Induced abortion was identified as follows: ICD-8 codes, 640, 641 and 642; ICD-10 codes, O04, O05 and O06 (Lohse et al., 2010). Second, to examine whether the associations were modified by parental psychiatric disorder before the childbirth, we performed analyses stratified by parental psychiatric disorders (yes, no). Third, to ascertain potential mediating effects of neonatal outcomes, we performed the analyses stratified by preterm birth, low birth weight, lower Apgar score at 5 min and SGA. Fourth, spontaneous abortions include missed abortions (ICD-8 codes: 6346 and 6451; ICD-10 code: O021) and other SAs (ICD-8 codes: 6438 and 6439; ICD-10 code: O03) (Lohse et al., 2010), which may represent different aetiology. To illustrate whether the associations differed by these two subtypes, we repeated the analyses individually. Fifth, concerning that the fertility treatment could also affect the risk of ADHD in offspring (Bay et al., 2013), we performed the analysis excluding children born to women with fertility problems (ICD-8 code: 628; ICD-10 code: N97) (Svahn et al., 2015). Sixth, we investigated whether maternal SA after the childbirth was associated with ADHD risk in offspring to examine the role of genetic susceptibility and stable family environment over time. Seventh, we restricted analyses to offspring born before 2010 to exclude children who might not be able to receive a diagnosis at very young ages. We also performed the analyses by including all children born from 1995 to 2016. Lastly, we used the multiple imputation procedure by chained equations to impute 10 replications to handle missing values of these covariates, including birth weight, Apgar score at 5 min, maternal smoking status during pregnancy, maternal education level and maternal cohabitation.

All statistical analyses were performed using Stata, version 15.1 (StataCorp).

Results

There were 130 206 (12.2%) children born to mothers who had at least one SA. Among those, 112 995 (10.6%) children were born to mothers with one SA before childbirth, and 17 211 (1.6%) children were born to mothers with at least two SAs before childbirth (Fig. 1). Table I presents the baseline characteristics of mothers and children in the exposed and unexposed groups. Compared with unexposed children, exposed children were more often born preterm and had lower birth weight and older parents. Mothers of the exposed children tended to smoke more during pregnancy, had a lower level of education and had higher comorbid diabetes or psychiatric disorders.

Table I Baseline characteristics of the study population using complete data (values are *n* (%)).

	Maternal spontaneous abortion (SA) status		
	No SA (*n* = 932 461)	**1 (*n* = 112 995)**	**≥2 (*n* = 17 211)**
Children's characteristics			
Gender			
Boys	478 682 (51.3)	57 818 (51.2)	8746 (50.8)
Girls	453 758 (48.7)	55 176 (48.8)	8465 (49.2)
Preterm (<37 weeks)			
No	888 379 (95.3)	106 913 (94.6)	15 873 (92.2)
Yes	44 082 (4.7)	6082 (5.4)	1388 (7.8)
Low birth weight (<2500 g)			
No	894 945 (96.0)	107 886 (95.5)	16 125 (93.7)
Yes	30 135 (3.2)	4156 (3.7)	947 (5.5)
Missing	7381 (0.8)	953 (0.8)	139 (0.8)
Apgar score 5 min			
10	858 364 (92.1)	104 166 (92.2)	15 858 (92.2)
7–9	61 648 (6.6)	7298 (6.5)	1087 (6.3)
0–6	6227 (0.6)	745 (0.6)	144 (0.8)
Missing	6222 (0.7)	777 (0.7)	122 (0.7)
Birth year			
1995–1998	202 215 (21.7)	27 325 (24.2)	4310 (25.0)
1999–2002	208 976 (22.4)	28 276 (25.0)	4700 (27.3)
2003–2006	211 180 (22.7)	25 110 (22.2)	3901 (22.7)
2007–2009	159 573 (17.1)	17 163 (15.2)	2373 (13.8)
2010–2012	150 517 (16.1)	15 121 (13.4)	1927 (11.2)
Parents' characteristics			
Maternal age at birth (years)			
≤25	191 221 (20.5)	12 589 (11.1)	1116 (6.5)
26–30	367 087 (39.3)	36 286 (32.1)	4357 (25.3)
31–35	285 078 (30.6)	43 788 (38.8)	6925 (40.2)
>35	89 075 (9.6)	20 332 (18.0)	4813 (28.0)
Paternal age at birth (years)			
≤25	96 232 (10.3)	6225 (5.5)	625 (3.6)
26–30	288 004 (30.9)	26 503 (23.5)	2998 (17.4)
31–35	321 543 (34.5)	41 593 (36.8)	6058 (35.2)
>35	218 755 (23.5)	38 028 (33.6)	7427 (43.2)
Missing	7927 (0.8)	646 (0.6)	103 (0.6)
Maternal smoking during pregnancy			
No	737 857 (79.1)	85 917 (76.0)	12 394 (72.0)
Yes	167 438 (18.0)	23 369 (20.7)	4191 (24.4)
Missing	27 166 (2.9)	3709 (3.3)	626 (3.6)
Maternal education level			
0–9	178 717 (19.2)	24 281 (21.5)	4670 (27.1)
10–14	435 954 (46.8)	52 094 (46.1)	7613 (44.2)
≥15	305 195 (32.7)	35 716 (31.6)	4746 (27.6)
Missing	12 595 (1.3)	904 (0.8)	182 (1.1)

(Continued)

Table I Continued.

	Maternal spontaneous abortion (SA) status		
	No SA (*n* = 932 461)	**1 (*n* = 112 995)**	**≥2 (*n* = 17 211)**
Paternal psychiatric disorder			
No	886 328 (95.1)	107 816 (95.4)	16 361 (95.1)
Yes	46 133 (4.9)	5179 (4.6)	850 (4.9)
Maternal psychiatric disorder			
No	876 883 (94.0)	105 975 (93.8)	16 052 (93.3)
Yes	55 578 (6.0)	7020 (6.2)	1159 (6.7)
Maternal diabetes status			
No	906 614 (97.2)	108 929 (96.4)	16 375 (95.1)
Yes	25 847 (2.8)	4066 (3.6)	836 (4.9)
Maternal original			
Born in Denmark	808 866 (86.8)	99 374 (87.9)	14 663 (85.2)
Not born in Denmark	123 451 (13.2)	13 617 (12.1)	2547 (14.8)
Maternal cohabitation			
Married	486 137 (52.1)	69 259 (61.3)	11 448 (66.5)
Not married	445 972 (47.8)	43 734 (38.7)	5762 (33.5)
Missing	352 (0.1)	<3	<3

A total of 25 747 children were identified as ADHD individuals (554 of mothers having at least two SAs, 3087 of mothers having one SA and 22 106 of mothers without SA). The mean age at first ADHD diagnosis was 10.4 years (SD 3.4). The incidence rates of ADHD were 3.17, 2.78 and 2.54 per 1000 person years in offspring whose mothers had at least two SAs, one SA and no SA, respectively. Overall, children of mothers with a history of SA had an increased rate of ADHD (HR, 1.11; 95% CI, 1.07 to 1.15). Compared to unexposed children, children of mothers with one SA had an increased rate of ADHD (HR, 1.09; 95% CI, 1.05 to 1.13) and those children of mothers with at least two SAs had a higher rate (HR, 1.22; 95% CI, 1.12 to 1.33) (as shown in Table II). A statistically significant trend for the association of number of maternal SA and ADHD risk in offspring ($HR_{0,1,2}$, 1.09, 95% CI, 1.06 to 1.12, $P < 0.001$) was observed.

The interaction between maternal history of SA and birth order was significant at the multiplicative scale (*P* for interaction term: <0.01). In the firstborn child, the risk of ADHD was consistently increased with the number of maternal SA, with a HR of 1.14 (95% CI, 1.07 to 1.23) in children of mothers with 1 SA before the childbirth and with a HR of 1.48 (95% CI, 1.23 to 1.78) in children of mothers with at least two SAs before the childbirth (as shown in Table III).

Adverse birth outcomes accounted for a very small proportion (0.1–3.6%) of the association between maternal SA and risk of ADHD, although almost all the natural indirect association estimates were marginally statistically significant (as shown in Table IV). Preterm birth was the strongest mediator that accounted for ~3.6% of the association.

Specifically, when maternal SA was dichotomized, maternal history of SA was associated with an increased risk of ADHD in offspring (OR, 1.22; 95% CI, 1.17 to 1.26). After accounting for misclassification of maternal SA by probabilistic bias analysis, the bias-corrected OR was 1.23 (95% CI, 1.18 to 1.27).

The population attributable fraction was 1.3%, indicating that maternal history of SA explained 1.3% of ADHD in the study population, if assuming an unconfounded causal association. For the bias analysis, the *E*-value for the observed overall estimate was 1.46.

The analyses stratified by offspring sex showed similar results (Supplementary Table SII). When we excluded induced abortion before the pregnancy, the estimates for the association were almost unchanged (Supplementary Table SIII). We observed a higher HR in children of parents with psychiatric disorders than that in children of parents without psychiatric disorders, although the increased rates in children whose mothers with at least two SAs and comorbid parental psychiatric disorders were not statistically significant (Supplementary Table SIV). Stratification analyses by adverse neonatal outcomes yielded similar results (Supplementary Table SV), so did analyses by different subtypes of SA (Supplementary Tables SVI and SVII) and analyses excluding the children with assisted reproductive technology (Supplementary Table SVIII). No significant association was observed between maternal SA that occurred after the childbirth and the risk of ADHD in offspring (Supplementary Table SIX). Results from sub-analyses restricted to offspring born before 2010 and to all offspring born from 1995 to 2016 were similar to those in primary analyses (Supplementary Tables SX and SXI). Analyses using multiple imputation also yielded similar results (Supplementary Table SXII).

Discussion

Principal findings

In this large population-based cohort study, we observed that maternal SA was associated with an 11% higher rate of ADHD in offspring, and the rate increased with the number of maternal SA, particularly

Table II Incidence rate and hazard ratios of attention-deficit/hyperactivity disorder according to maternal history of SA status ($n = 1\,062\,667$).

Maternal history of SA	ADHD		Adjusted HR (95% CI)			
	n	Rate per 1000 person years	Model 1	Model 2	Model 3	Model 4
No ($n = 932\,461$)	22 106	2.54	1.00 Ref	1.00 Ref	1.00 Ref	1.00 Ref
Yes ($n = 130\,206$)	3641	2.82	1.10 (1.06 to 1.14)	1.12 (1.08 to 1.16)	1.11 (1.07 to 1.15)	1.11 (1.07 to 1.15)
1 SA ($n = 112\,995$)	3087	2.78	1.08 (1.04 to 1.12)	1.10 (1.06 to 1.14)	1.09 (1.05 to 1.14)	1.09 (1.05 to 1.13)
≥2 SAs ($n = 17\,211$)	554	3.17	1.23 (1.13 to 1.33)	1.25 (1.14 to 1.36)	1.23 (1.13 to 1.34)	1.22 (1.12 to 1.33)

Model 1 adjusted for birth year, sex; Model 2 additionally adjusted for parity, maternal variables (age, smoking during pregnancy, education level, origin, cohabitation) and paternal age; Model 3 additionally adjusted for parental psychiatric disorders, maternal hypothyroidism and diabetes; Model 4 additionally adjusted for low birth weight (<2500 g), preterm birth (<37 gestational weeks), low Apgar score at 5 min (<7) and small for gestational age (birth weight below the 10th percentile for infants of the same gestational age and sex).
HR, hazard ratio; ADHD, attention-deficit/hyperactivity disorder.

Table III Incidence rate and HRs of ADHD according to maternal SA status stratified by birth order ($n = 1\,062\,667$).

Maternal history of SA	Birth order					
	Firstborn children			Non-firstborn children		
	ADHD (*n*)	Rate	Adjusted HR (95% CI)*	ADHD (*n*)	Rate	Adjusted HR (95% CI)*
No	10 679	2.62	1.00 Ref	11 427	2.46	1.00 Ref
Yes	1021	3.04	1.17 (1.10 to 1.26)	2620	2.75	1.09 (1.04 to 1.13)
1 SA	902	2.97	1.14 (1.07 to 1.23)	2185	2.69	1.07 (1.02 to 1.12)
≥2 SAs	119	3.70	1.48 (1.23 to 1.78)	435	3.05	1.17 (1.06 to 1.30)

*Analyses are adjusted for birth year, sex, maternal smoking during pregnancy, maternal education level, maternal country of origin, maternal cohabitation, parental age, parental psychiatric disorders, maternal hypothyroidism, maternal diabetes and neonatal adverse outcomes including low birth weight (<2500 g), preterm birth (<37 gestational weeks), low Apgar score at 5 min (<7) and small for gestational age (birth weight below the 10th percentile for infants of the same gestational age and sex).

for the firstborn child. Our findings suggested that the observed associations were independent of a number of factors, such as maternal socioeconomic status, type of SA, parental history of psychiatric disorders, pregnancy characteristics (maternal smoking status, infection, diabetes and hypothyroidism status during pregnancy) and birth outcomes (low birth weight, preterm birth, low Apgar score and SGA).

Previous studies have investigated the association of maternal history of SA with neonatal outcomes, such as preterm birth, low birth weight, stillbirth and small for gestational age in the subsequent pregnancies with short-term follow-up (Xiong *et al.*, 2002; Weintraub *et al.*, 2005; Bhattacharya *et al.*, 2008; Klemetti *et al.*, 2012; Gunnarsdottir *et al.*, 2014; Makhlouf *et al.*, 2014; Ahrens *et al.*, 2016). One US study of 21 277 women reported that the risks of preterm birth, low birth weight and stillbirth in the next pregnancy were increased with the number of previous spontaneous abortions (Ahrens *et al.*, 2016). Another Danish study of 619 587 women also showed that maternal history of two or more SAs was associated with increased risks of preterm birth, small for gestational age infants and stillbirth in subsequent pregnancy (Gunnarsdottir *et al.*, 2014). Birth outcomes, such as preterm birth, low birth weight and low Apgar score, could be considered as potential mediators in the pathway from maternal SA and ADHD in offspring (Biederman, 2005). However, findings from our study showed that the elevated rates of ADHD in offspring were not attenuated by the exclusion of children with these birth outcomes. Mediation analyses further indicated that adverse birth outcomes could only explain a very small proportion of the overall associations. This may suggest an aetiological role of maternal SA on ADHD in offspring. SA has been proposed as a marker of genetic susceptibility to psychiatric disorders in mothers and offspring (Fergusson *et al.*, 2008; Toffol *et al.*, 2013); however, we did not observe an association between maternal SA after the childbirth and the ADHD risk in offspring, indicating that prenatal adverse environmental exposure could play an important role on long-term mental health including ADHD.

Our findings indicated that the association between maternal history of SA and rate of ADHD in offspring was greater in the firstborn child. A study in the USA (791 live-born offspring with 385 women) had also suggested that a history of SA was associated with a 4-fold risk of epilepsy in offspring, and the risk was particularly high in the firstborn child (Schupf and Ottman, 2001). Previous studies have showed that the risk of pregnancy complications was increased among primigravida women, compared with women with a previous live birth (Jivraj *et al.*, 2001; Magnus *et al.*, 2019). A live birth seems to reduce the negative outcomes of pregnancy losses prior to the childbirth (Egerup *et al.*,

Table IV Mediation analysis with adverse birth outcomes as potential mediators between maternal history of SA and risk of ADHD in offspring (n = 1 062 667).

Variables	Odds ratio (95% CI)[a]
Low birth weight	
Natural direct effect	1.219 (1.151 to 1.295)
Natural indirect effect	1.007 (1.001 to 1.009)
Total effect	1.228 (1.160 to 1.304)
Proportion, %[b]	3.56
Preterm birth	
Natural direct effect	1.219 (1.154 to 1.291)
Natural indirect effect	1.008 (1.006 to 1.010)
Total effect	1.228 (1.162 to 1.302)
Proportion, %	3.84
Low Apgar score	
Natural direct effect	1.234 (1.167 to 1.312)
Natural indirect effect	1.000 (1.000 to 1.001)
Total effect	1.235 (1.167 to 1.313)
Proportion, %	0.10
Small for gestational age	
Natural direct effect	1.229 (1.164 to 1.305)
Natural indirect effect	1.000 (1.000 to 1.001)
Total effect	1.230 (1.164 to 1.305)
Proportion, %	0.11

[a]adjusted for sex, birth year, parity, parental age, maternal smoking during pregnancy, maternal education level, maternal country of origin, maternal cohabitation, parental psychiatric disorders, maternal hypothyroidism and maternal diabetes.
[b]proportion mediated was calculated as log (natural indirect relationship)/log (total relationship).

2016). Our data suggested that primigravida women with a history of SA gave birth to children with the highest risk of ADHD. We also observed a more pronounced increase of ADHD rate in children whose mothers with SA and comorbid parental psychiatric disorders, indicating an added influence of genetic susceptibility.

There may be two plausible pathways underlying our observations. First, foetal programming could be one possible pathway of maternal history of SA leading to ADHD in offspring. Women with a history of SA were more likely to experience elevated levels of stress in the next pregnancy (Fergusson *et al.*, 2008), which could activate the hypothalamic–pituitary–adrenal axis of pregnant women (Tsigos and Chrousos, 2002). The activation of the hypothalamic–pituitary–adrenal axis may impair placental function and downregulate the activity of placental 11β-HSD-2, decreasing the protection of this 'barrier' (Seckl and Holmes, 2007). As a result, increased maternal cortisol can cross the placenta, leading to an increased cortisol level in the foetal circulation (Seckl and Holmes, 2007). Elevated levels of foetal cortisol might play a permanent detrimental role in foetal brain development, leading to an increased risk of all mental disorders including hyperactive, behavioural and emotional disorders later in life (Bale *et al.*, 2010, Lewis *et al.*, 2014). Another potential biological pathway could be hypoxic status in pregnancy resulting from previous SA (Renaud *et al.*, 2011). Hypoxic conditions have adverse consequences on foetal brain development and are associated with an increased risk of ADHD in children (Getahun *et al.*, 2013).

Strengths and limitations of this study

Our study has several methodological strengths. First, the comprehensive administrative database allowed us to access pregnancy information that was actually obtained in an objective manner, which reduced the chance of recall bias. Moreover, this study was based on the national register data with nearly complete follow-up, thus minimizing the possibility of misclassification bias. Second, the diagnosis of SA has been validated and confirmed in the Danish Patient Register and the distributions of women with one SA and ≥2 SAs are comparable with those from other studies (Lohse *et al.*, 2010). Third, ADHD was identified from both hospital medical record and prescription database (Pottegård *et al.*, 2012). The combination of hospitalization registers and prescription data allowed us to identify individuals with both mild and severe ADHD symptoms.

Several limitations need to be noted. First, even though we used population-based register data to capture maternal history of SA, misclassification should also be taken into account. SA is a common pregnancy outcome, but it is challenging to estimate the precise rate, especially for the earlier pregnancy losses when women may not even be aware that they are pregnant (Wilcox *et al.*, 1988). But the misclassification of maternal SA is most likely to be non-differential, as the diagnosis of SA is made without any knowledge of the outcome (ADHD in offspring in this study). As shown in previous studies (Wilcox *et al.*, 1988; Ahrens *et al.*, 2016), this would lead to reduced statistical power and may bias the estimate towards the null. Findings from the probability sensitivity analyses indicate that only around 1% of change in the estimate was due to misclassification of SA. Second, previous studies have suggested that adverse pregnancy and neonatal outcomes were often worse following a second trimester SA (Edlow *et al.*, 2007). However, we do not have detailed clinical information on the gestational age of pregnancy termination; thus, we were unable to distinguish between the association of SA occurring at different stages of pregnancy and the risk of ADHD. Third, even though we have adjusted for a wide variety of potential confounders, the residual confounding from unidentified confounders and unmeasured confounders, such as maternal inflammation response, is still possible, which might cause an overestimate of the true association. Nevertheless, additional adjustment for maternal infection during pregnancy did not change the results (results not shown). Using the calculated *E*-value, an unmeasured confounder would need to be associated with maternal SA and the ADHD risk in offspring by a magnitude of 1.46 or above and beyond the measured confounders to explain away the observed association, so it is unlikely that our association could be explained away by an unmeasured confounder (VanderWeele and Ding, 2017).

Conclusion

Our findings suggest that maternal history of SA is associated with an increased rate of ADHD in offspring, and the rate increases with the number of maternal SA. These findings are consistent when taking into consideration of a number of maternal and offspring characteristics,

as SA is quite frequent (varying from 15 to 20%) and a small increase of neurodevelopmental problems in offspring could have major public health implications.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

H.W. and F.L. performed the literature review, conducted data analyses and drafted the manuscript. M.M., Y.Y., H.J., H.L., R.H. and C.O. contributed to the interpretation of the data, critical revision of the paper and approval of the final version. J.L. and J.Z. are the guarantors. They developed the study conception, directed the analytic strategy of the study and supervised the drafting of the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflict of interest

None declared.

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