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ORIGINAL REPORT

Exposure to reactive intermediate-inducing drugs during pregnancy and the incident use of psychotropic medications among children

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ABSTRACT

Purpose Our study aimed to investigate the association between prenatal exposure to reactive intermediate (RI)-inducing drugs and the initiation of psychotropic medications among children.

Methods We designed a cohort study using a pharmacy prescription database. Pregnant women were considered exposed when they received a prescription of RI-inducing drugs. These drugs could be either used alone (RI+/FAA−) or combined with drugs exhibiting folic acid antagonism (FAA, RI+/FAA+). The reference group included pregnant women who did not receive any RI-inducing drugs or FAA drugs.

Results We analyzed 4116 exposed and 30 422 reference pregnancies. The hazard ratio (HR) with 95% confidence interval (CI) was 1.27 (95%CI 1.15–1.41) for pregnancies exposed to RI-inducing drugs as a whole. Considering subgroups of RI-inducing drugs, prenatal exposure to both RI+/FAA+ and RI+/FAA− was associated with the children's initiation of psychotropic medications, HRs being 1.35 (95%CI 1.10–1.66) and 1.26 (1.13–1.41), respectively. The HRs were increased with prolonged exposure to RI-inducing drugs, especially in the first and second trimesters. In a detailed examination of the psychotropics, the incidences of receiving antimigraine preparations and psychostimulants were significantly increased for the exposed children, compared with the reference children. The incidences of receiving antipsychotics and hypnotics were also higher for the exposed children; however, the HRs did not reach significance after adjustment.

Conclusions We found a significantly increased incident use of psychotropic medications among children prenatally exposed to RI-inducing drugs, especially during the first and second trimesters. This suggests a detrimental effect during critical periods of brain development.

KEY WORDS—reactive intermediates; folic acid antagonism; pregnancy; drug exposure; psychotropic medications; pharmacoepidemiology

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INTRODUCTION

Drugs can exert their teratogenicity through a reactive intermediate (RI)-mediated mechanism. This mechanism involves the bioactivation of a relatively nontoxic drug into electrophilic/free radical RIs and reactive oxygen species (ROS), which damage cellular macromolecules or alter signal transduction. However, there are other counteracting pathways: the detoxification of cellular antioxidants and detoxifying enzymes and the self-repair of oxidative damage.[1] An imbalance towards increased RIs and ROS may adversely affect the fetus.

Experimental studies found widespread neuronal death in the developing brain under ROS-induced conditions (e.g., hypoxia and high glucose concentrations).[2,3] Additionally, the use of ionizing radiation as a source of RI and ROS generation in adult mice showed that the brain was the most vulnerable among all other tissues.[4] Besides, human studies have added the role of increased oxidative markers in various nervous system disorders,[5–7] whereby environmental factors and genetic alterations in redox enzymes may share a role.

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We therefore hypothesized that prenatal exposure to RI-inducing drugs might have an effect on the child's nervous system. We set out to examine the incident use of psychotropic medications (as a proxy for the effect on the nervous system) among the exposed and reference children. Because folates (folic acid and its derivatives) may act as free radical scavengers or link to the metabolism of the cellular antioxidant glutathione,[8,9] folates may be associated with the detoxification process. We thereby explored the exposure to drugs exhibiting folic acid antagonism (FAA) in addition to RI-inducing-drugs.

METHODS

Design and setting

Our cohort study used the pregnancy database, which is part of the pharmacy prescription database (IADB.nl) holding prescription records of approximately 600 000 patients in the Northern Netherlands. Because of the high patient pharmacy loyalty in the Netherlands, the prescription records for each patient in the database are virtually complete, except for over-the-counter (OTC) drugs and drugs dispensed during hospitalization.[10]

The pregnancy database was generated by linking a mother to her child using an address code as previously described.[11] Approximately 65% of the children in the main IADB database could be linked to their mothers, and validation showed 99% accuracy.[11]

Because we only used unidentifiable pre-existing data, ethical approval was not needed.

Study population

We included pregnancies with children born between 1994 and 2011. Pregnancies were excluded if they resulted in twins/multiple births (i.e., more than one child born on the same date and at the same address with one possible mother). Pregnancies were also excluded if they had less than 12 months of maternal data prior to the child's birth or less than 36 months of child data, or if they were exposed to FAA drugs only (RI−/FAA+). When we compared the RI+/FAA + exposure group with the reference group (see section on Exposure definations and Figure 1), we excluded pregnancies that were not exposed to RI-inducing drugs and FAA drugs in the same trimester. Figure 1 shows the flow diagram of the study population. Depending on the sensitivity analyses, we considered other exclusion criteria (see section on Sensitivity analyses).

Exposure

Drug identification. Because RIs are not stable enough to be transported from the mother to the fetus, they must be generated within the fetus to exert a teratogenic effect.[1] Although a dose–response relationship has been suggested for teratogens, a dose threshold for the teratogenicity of most drugs has not been determined. To identify RI-inducing drugs, we first listed all drugs used by pregnant women in the database. We cross-referenced these drugs against previously compiled lists of drugs that are known to be bioactivated into RIs and ROS (Supporting information). We selected 48 drugs with systemic absorption and with a defined daily dose (DDD) ≥50 mg (based on http://www.whocc.no/atc_ddd_index/) as RI-inducing drugs (Table S1). The cut-off value of 50 mg was chosen on the basis of the relationship between daily dose and idiosyncratic adverse drug reactions (IADRs)[12,13]: (1) IADRs mainly resulted from conjugates of an electrophilic RI of a drug with cellular macromolecules; and (2) more than 90% of drugs with black box warning for IADRs have a DDD ≥50 mg. Thus, we used the cut-off value of 50 mg to select drugs with a higher burden of RI and ROS generation, making them more likely to be associated with RI-mediated adverse effects.

We identified FAA drugs using the list of van Gelder[14] and the current Pubmed entries of "Folic Acid Antagonists" (Pharmacological Action). Additionally, we searched the whole PubMed database up to August 2015, using the terms "Folic Acid Antagonists"[Mesh] AND Review[ptyp]. This resulted in 608 citations from which one additional FAA drug (proguanil) was found. In total, 14 FAA drugs were used in the pregnancy database. Eight drugs have both RI-inducing and FAA properties (sulfasalazine, trimethoprim, phenobarbital, primidone, phenytoin, carbamazepine, valproic acid, and lamotrigine) (Table S2).

Exposure definitions. Because information on the conception date was unavailable, we used a standardized period of 273 days to define pregnancy duration (91 days for each trimester) as previously described.[15] The exposed group included women who received a prescription of RI-inducing drugs at any time during pregnancy or received a prescription of RI-inducing drugs before pregnancy, but the duration of the treatment lasted into pregnancy. The reference group included women who did not receive any RI-inducing drugs or FAA drugs during pregnancy.

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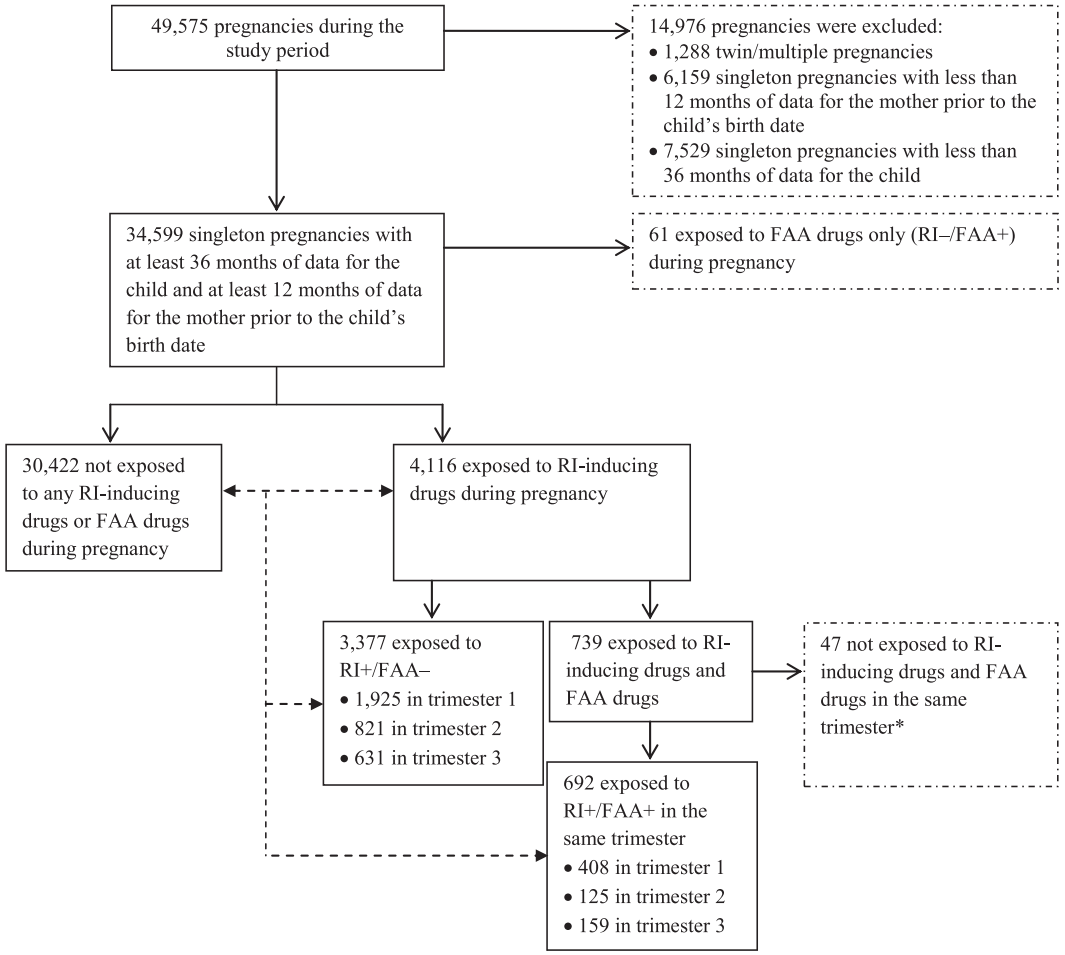

Figure 1. Flow diagram of the study population

We also investigated exposure to RI-inducing drugs in each trimester. Exposure in the second trimester excluded women who had a prior exposure in the first trimester, and exposure in the third trimester excluded women who had a prior exposure in the first and second trimesters.

Similarly, we investigated two different FAA exposure categories: exposure to the combination of RI-inducing and FAA drugs (RI+/FAA+) and exposure to RI-inducing drugs only (RI+/FAA–). The RI+/FAA+ category included eight drugs with both RI-inducing and FAA properties, and/or an RI-inducing drug only (RI+/FAA−) combined with an FAA drug only (RI−/FAA+) in the same trimester.

Finally, we stratified the exposure into three standardized levels of DDDs of RI-inducing drugs: ≤3DDDs, 3–14DDDs (this category does not include 3DDDs) and >14DDDs. This categorization was used to distinguish short-term use from prolonged use.

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Outcome

The outcome of interest was the incident use of psychotropic medications among children (since their birth). The incident use of psychotropic medications was identified as the child received at least two consecutive prescriptions of psychotropic drugs in the year after the index date (the date on which the child received his or her first prescription of psychotropic drugs). This was to ensure that we were looking at "regular" users rather than a single event or a misdiagnosis. The psychotropic drugs included antiepileptics (Anatomical Therapeutic Chemical (ATC) code N03), antimigraine preparations (N02C), antipsychotics (N05A), anxiolytics (N05B), hypnotics (N05C), antidepressants (N06A and N06CA), and psychostimulants (N06B and N06CB). Lithium salts and anti-dementia drugs were not used by our children.

Statistical analysis

Descriptive statistics were used to describe characteristics of the exposed and reference groups, including maternal age at delivery, maternal diabetes (defined as the pregnant women receiving a prescription of antidiabetic medications, ATC code A10), the total number of medications taken by the pregnant woman, and child's gender and age on the index date.

The incidence rate of the children's use of psychotropic medications was calculated as the number of users divided by the total follow-up time (in years). The follow-up time was defined as the time from the child's birth date until the index date or until the date of the last update of the database, whichever occurred first. Cox proportional hazards regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) of the incident use of psychotropic medications among children. The assumption of proportional hazards was assessed graphically using stratified analysis. All exposure categories (i.e., RI-inducing drugs with and without FAA drugs and exposure by trimesters) were individually compared with the reference group. HRs were adjusted for maternal age and diabetes because of their potential relation to ROS.[16,17] HRs were also adjusted for the total number of medications taken by the pregnant woman, which was used as a proxy for their "healthcare-seeking" behavior and/or frequent approach to the healthcare system that might increase the chance for their children to be examined and thus be treated with psychotropic medications. To minimize statistical instability, we did not calculate HRs if fewer than five outcomes per predictor variable were observed in the exposed or reference group.[18]

All analyses were performed in SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). A p-value <0.05 and a 95%CI not containing 1 were considered statistically significant.

Sensitivity analyses

We performed different sensitivity analyses because of the following reasons:

Because our exposure definitions were based on 48 RI-inducing drugs, it is possible that the association with the children's initiation of psychotropic medications was driven by a dominant drug/drug class with its own teratogenic effect that does not pertain to RI-inducing mechanism. We therefore examined 48 RI-inducing drugs individually.

Because maternal use of nervous system drugs (and/or maternal exacerbation of psychiatric diseases) may pharmacologically affect fetal brain, we performed a subset analysis by excluding pregnancies, which received nervous system drugs (ATC code N01A, N02, N03, N04, N05, N06, and N07) (Figure S1).

Because an occasional prescription of RI-inducing drugs might not be used by pregnant women, we applied a stricter criterion to define exposure as when the pregnant women received at least two prescriptions of RI-inducing drugs.

Because we used the cut-off value of ≥50 mg to select RI-inducing drugs, exposure to drugs with potential RI biotransformation but with a DDD <50 mg (Table S3) might have been misclassified by our approach and could bias the results. We reanalyzed data by excluding pregnancies exposed to these drugs unless they were concurrently exposed to RI-inducing drugs.

Finally, because we think that RI-inducing drugs might have a lasting effect on the nervous system once being used in early pregnancy, we excluded women who had a prior exposure in the definitions of exposure in the second and third trimesters (see section on Exposure definitions). However, this might underestimate the effect of the second and third trimesters and may have led to an exclusive association with the early months if the women took RI-inducing drugs throughout pregnancy. Therefore, to examine the role of each trimester, we performed a subset analysis on pregnancies exposed in the first trimester only, the second trimester only, and the third trimester only.

RESULTS

There were 34 599 singleton pregnancies in the source population. Of these, 4116 pregnancies exposed to RI-

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inducing drugs were selected as the exposed group, and 30 422 pregnancies that were not exposed to any RI-inducing drugs or FAA drugs were selected as the reference group. Their characteristics are shown in Table 1. Women in the exposed group were slightly younger at the time of their delivery. The prevalence of treated diabetes and the total number of medications taken during pregnancy were, however, twice as high among the exposed women compared with the reference women. Types of medications used by the pregnant women are described in Table S4. Boys accounted for half of children born in each group. The child's age on the index date was similar in both groups.

On the basis of the inclusion criteria, children born in the exposed and reference groups had at least 36 months of data for the analyses. They also had comparable follow-up time with a median of 8.3 vs. 8.3 years and a maximum of 19.8 vs. 19.9 years, respectively. During follow-up, psychotropic medications were used by 3192 children (509 in the exposed group and 2683 in the reference group). On the index date, the majority of children received psychostimulants (69.2%), followed by antipsychotics (7.3%), anxiolytics (7.0%), antiepileptics (5.7%), hypnotics (4.3%), antidepressants (3.6%), and antimigraine preparations (3.0%).

Compared with the reference group, children prenatally exposed to RI-inducing drugs were more likely to receive psychotropic medications (Table 2), HR 1.27 (95%CI 1.15–1.41). The HRs significantly increased in both exposure categories RI+/FAA+ and RI+/FAA−, being 1.35 (95%CI 1.10–1.66) and 1.26 (95%CI 1.13–1.41), respectively. Within the RI+/FAA+ category, the association was found with prenatal exposure to both antiepileptics and non-antiepileptics (Table S5).

A detailed examination of the psychotropic drugs (Table S6) showed that children prenatally exposed to RI-inducing drugs were more likely to receive antimigraine preparations and psychostimulants than the reference children, HRs being 2.51 (95%CI 1.54–4.10) and 1.25 (95%CI 1.10–1.42), respectively. The incidences of receiving antipsychotics and hypnotics were also higher for the exposed children; however, the HRs did not reach significance after adjustment.

When we stratified the exposure by total DDD amount, the increased incident use of psychotropic medications among children was associated with prolonged exposure to RI-inducing drugs (Table 3), the highest HR being 1.42 (95%CI 1.19–1.69) for >14DDDs. It is noteworthy that prenatal exposure to a short course of ≤3DDDs was not associated with the children's initiation of psychotropic medications.

When we examined 48 RI-inducing drugs individually (Table 4), elevated HRs were found with most drugs, which seem to be a generalized effect.

In the subset of women who did not use nervous system drugs during pregnancy (Figure S1 and Table S7), the incidence of receiving psychotropic medications among their children also significantly increased with exposure to RI-inducing drugs.

In addition to the main results in Table 2, three sensitivity analyses were performed: one with a stricter exposure definition (more than or equal to two prescriptions of RI-inducing drugs) (Table S8), one with the exclusion of pregnancies exposed to drugs with potential RI biotransformation but with a DDD <50 mg (Table S9), and one examining role of each trimester exclusively (Table S10). Briefly, we found an association between prenatal exposure to RI-inducing drugs and the children's initiation of psychotropic medications, especially if the exposure was in the first and second trimesters.

Table 1. Characteristics of exposed and reference pregnancies

	Reference*	Any RI		RI+/FAA+		RI+/FAA–	
	n = 30 422	*n* = 4116	*p*	*n* = 692	*p*	*n* = 3377	*p*
Mother							
Age at delivery (years), mean ± SD	30.6 ± 4.6	30.3 ± 5.0	**<0.001**	30.0 ± 5.0	**0.002**	30.3 ± 5.0	**0.001**
Diabetes,† *n* (%)	218 (0.7)	65 (1.6)	**<0.001**	10 (1.4)	**0.026**	54 (1.6)	**<0.001**
Total number of medications,‡ mean ± SD	2.2 ± 2.1	5.0 ± 3.1	**<0.001**	5.1 ± 3.0	**<0.001**	4.9 ± 3.1	**<0.001**
Child							
Boys, *n* (%)	15 596 (51.3)	2097 (50.9)	0.700	327 (47.3)	0.442	1708 (50.6)	0.447
Age (years) on index date, mean ± SD	8.4 ± 3.6	8.4 ± 3.8	0.822	8.2 ± 3.9	0.541	8.4 ± 3.8	0.860

*The reference group included pregnancies not exposed to any reactive intermediate (RI)-inducing drugs or drugs exhibiting folic acid antagonism (FAA).
†Insulin therapy was used by 60 of 65 mothers exposed to RI-inducing drugs and by all reference mothers with diabetes.
‡The total number of medications taken by the pregnant woman during pregnancy.
Any RI, any RI-inducing drugs; RI+/FAA+, drugs with both RI-inducing and FAA properties, or RI-inducing drugs only combined with FAA drugs only; RI+/FAA−, RI-inducing drugs only; SD, standard deviation.
Significant values are in bold.

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Table 2. Incidence rates (IRs) and hazard ratios (HRs) of the use of psychotropic medications among children prenatally exposed to reactive intermediate (RI)-inducing drugs

	N	Pregnancies with outcome *n* (%)	IR (per 1000 person-years)	HR (95%CI)	Adjusted HR (95%CI)
Reference*	30 422	2683 (8.8)	9.79	1	1
Exposed during pregnancy					
Any time in pregnancy					
Any RI	4116	509 (12.4)	13.71	**1.39 (1.26–1.53)**	**1.27 (1.15–1.41)**
RI+/FAA+	692	99 (14.3)	15.09	**1.48 (1.21–1.80)**	**1.35 (1.10–1.66)**
RI+/FAA−	3377	403 (11.9)	13.37	**1.37 (1.23–1.52)**	**1.26 (1.13–1.41)**
Trimester 1					
Any RI	2367	290 (12.3)	13.64	**1.39 (1.23–1.57)**	**1.27 (1.12–1.45)**
RI+/FAA+	408	63 (15.4)	16.58	**1.65 (1.28–2.11)**	**1.50 (1.17–1.94)**
RI+/FAA–	1925	222 (11.5)	12.92	**1.32 (1.15–1.52)**	**1.22 (1.01–1.41)**
Trimester 2					
Any RI	958	130 (13.6)	14.97	**1.51 (1.26–1.80)**	**1.40 (1.17–1.67)**
RI+/FAA+	125	20 (16.0)	15.78	1.48 (0.95–2.29)	1.38 (0.89–2.14)
RI+/FAA–	821	108 (13.2)	14.80	**1.51 (1.25–1.83)**	**1.41 (1.16–1.71)**
Trimester 3					
Any RI	791	89 (11.3)	12.41	**1.25 (1.01–1.54)**	1.18 (0.95–1.46)
RI+/FAA+	159	16 (10.1)	10.72	1.05 (0.64–1.72)	—[†]
RI+/FAA−	631	73 (11.6)	12.87	**1.30 (1.03–1.64)**	1.24 (0.98–1.57)

*The reference group included pregnancies not exposed to any RI-inducing drugs or drugs exhibiting folic acid antagonism (FAA).
[†]The HRs were not calculated because of the possibility of statistical instability (fewer than five outcomes per predictor variable in the exposed group).
Any RI, any RI-inducing drugs; RI+/FAA+, drugs with both RI-inducing and FAA properties, or RI-inducing drugs only combined with FAA drugs only; RI+/FAA−, RI-inducing drugs only; HRs were adjusted for maternal age, maternal diabetes, and the total number of medications taken by the pregnant woman; CI, confidence interval.
Significant values are in bold.

Table 3. Incidence rates (IRs) and hazard ratios (HRs) of the use of psychotropic medications among children prenatally exposed to reactive intermediate (RI)-inducing drugs, stratified into three standardized levels of defined daily doses (DDDs)

	N	Pregnancies with outcome *n* (%)	IR (per 1000 person-years)	HR (95%CI)	Adjusted HR (95%CI)
Reference*	30 422	2683 (8.8)	9.79	1	1
Exposed during pregnancy					
≤3DDDs	292	51 (13.7)	10.72	0.99 (0.70–1.40)	0.90 (0.63–1.27)
3–14DDDs[†]	2700	307 (11.8)	13.56	**1.39 (1.24–1.55)**	**1.27 (1.12–1.43)**
>14DDDs	1124	151 (13.2)	14.98	**1.53 (1.30–1.81)**	**1.42 (1.19–1.69)**

*The reference group included pregnancies not exposed to any reactive intermediate-inducing drugs or drugs exhibiting folic acid antagonism.
[†]This category did not include the value of 3DDDs.
HRs were adjusted for maternal age, maternal diabetes, and the total number of medications taken by the pregnant woman.
CI, confidence interval.
Significant values are in bold.

DISCUSSION

Summary of findings and relation to literature

Our prescription-based cohort study found that prenatal exposure to RI-inducing drugs was associated with an increased incident use of psychotropic medications among children. This association remained when we restricted the analysis to pregnant women who did not receive any nervous system drugs. This suggests that the association was not confounded by maternal use of nervous system drugs (and/or maternal exacerbation of psychiatric diseases).

We could not investigate the potential interaction of RIs and FAA in pregnancies exposed to RI+/FAA− drugs combined with RI−/FAA+ drugs because the majority of pregnancies was exposed to the eight drugs with both RI-inducing and FAA properties (only five pregnancies were exposed to the combination of RI+/FAA− and RI−/FAA+ drugs).

The increased incident use of psychotropic medications among children exposed to RI-inducing drugs during the first and second trimesters is consistent with the pattern of fetal development. While the brain develops over the entire pregnancy, the first and second trimesters are critical periods for most brain regions.[3] The higher HR following exposure in the second trimester could be explained by the development of human metabolizing enzymes that convert drugs into RIs. In early pregnancy, drug metabolism primarily relies on enzymes with, or associated with, peroxidase activities. As pregnancy progresses, levels of many cytochromes P450 increase,[1,19] and thus, drug

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Table 4. Incidence rates (IRs) and hazard ratios (HRs) of the use of psychotropic medications among children prenatally exposed to 48 reactive intermediate (RI)-inducing drugs

	N	Pregnancies with outcome *n* (%)	IR (per 1000 person-years)	HR (95%CI)	Adjusted HR (95%CI)
Reference*	30 422	2683 (8.8)	9.79	1	1
Exposed to RI-inducing drugs during pregnancy[†]	4116	509 (12.4)	13.71	**1.39 (1.26–1.53)**	**1.27 (1.15–1.41)**
Sulfasalazine	27	1 (3.7)	3.96	—[‡]	—[‡]
Tolbutamide	2	1 (50.0)	46.78	—[‡]	—[‡]
CVD[§]	87	12 (13.8)	15.61	1.62 (0.92–2.85)	—[‡]
Clopidogrel	1	0 (0.0)	0	—[‡]	—[‡]
Amiodarone	1	1 (100.0)	183.97	—[‡]	—[‡]
Spironolactone	2	0 (0.0)	0	—[‡]	
Propranolol	70	11 (15.7)	17.67	**1.81 (1.00–3.27)**	—[‡]
Verapamil	8	0 (0.0)	0	—[‡]	—[‡]
Diltiazem	1	0 (0.0)	0	—[‡]	—[‡]
Captopril	1	0 (0.0)	0	—[‡]	—[‡]
Losartan	3	0 (0.0)	0	—[‡]	—[‡]
Gemfibrozil	1	0 (0.0)	0	—[‡]	—[‡]
Terbinafine	28	3 (10.7)	13.56	—[‡]	—[‡]
Raloxifene	1	0 (0.0)	0	—[‡]	—[‡]
Propylthiouracil	27	2 (7.4)	8.35	—[‡]	—[‡]
Minocycline	8	0 (0.0)	0	—[‡]	—[‡]
Trimethoprim	587	87 (14.8)	15.41	**1.49 (1.20–1.84)**	**1.35 (1.09–1.68)**
Clarithromycin	42	1 (2.4)	3.03	—[‡]	—[‡]
Nitrofurantoin	1509	161 (10.7)	14.31	**1.75 (1.49–2.05)**	**1.60 (1.35–1.88)**
Ketoconazole	2	0 (0.0)	0	—[‡]	—[‡]
Rifampicin	2	0 (0.0)	0	—[‡]	—[‡]
Isoniazid	4	0 (0.0)	0	—[‡]	—[‡]
Dapsone	2	0 (0.0)	0	—[‡]	—[‡]
Nevirapine	3	0 (0.0)	0	—[‡]	—[‡]
Cyclophosphamide	1	0 (0.0)	0	—[‡]	—[‡]
Procarbazine	1	0 (0.0)	0	—[‡]	—[‡]
NSAIDs[¶]	1078	148 (13.7)	14.61	**1.44 (1.22–1.70)**	**1.35 (1.14–1.60)**
Indometacin	24	4 (16.7)	15.80	—[‡]	—[‡]
Diclofenac	473	62 (13.1)	14.68	**1.51 (1.17–1.94)**	**1.42 (1.10–1.84)**
Ibuprofen	418	57 (13.6)	14.32	**1.41 (1.08–1.82)**	**1.34 (1.03–1.75)**
Naproxen	205	33 (16.1)	16.02	**1.49 (1.05–2.09)**	1.40 (0.99–1.98)
Paracetamol	822	117 (14.2)	12.79	1.11 (0.92–1.34)	1.01 (0.83–1.23)
AEDs**	119	17 (14.3)	16.45	**1.75 (1.09–2.82)**	—[‡]
Phenobarbital/Primidone[††]	2	0 (0.0)	0	—[‡]	—[‡]
Phenytoin	4	0 (0.0)	0	—[‡]	—[‡]
Carbamazepine	72	12 (16.7)	18.38	**1.89 (1.07–3.33)**	—[‡]
Valproic acid	47	7 (14.9)	16.52	1.66 (0.79–3.49)	—[‡]
Lamotrigine	14	1 (7.1)	10.06	—[‡]	—[‡]
Thioridazine	4	0 (0.0)	0	—[‡]	—[‡]
Antidepressants[‡‡]	157	22 (14.0)	15.71	**1.60 (1.05–2.43)**	1.49 (0.97–2.28)
NSRIs[§§]	146	21 (14.4)	15.78	**1.58 (1.03–2.43)**	1.48 (0.96–2.29)
Imipramine	6	3 (50.0)	66.50	—[‡]	—[‡]
Clomipramine	54	7 (13.0)	13.77	1.36 (0.65–2.85)	—[‡]
Amitriptyline	84	10 (11.9)	13.01	1.29 (0.70–2.41)	—[‡]
Nortriptyline	4	1 (25.0)	48.26	—[‡]	—[‡]
Mianserin	1	1 (100.0)	77.91	—[‡]	—[‡]
Trazodone	2	0 (0.0)	0	—[‡]	—[‡]
Nefazodone	3	0 (0.0)	0	—[‡]	—[‡]
Duloxetine	6	0 (0.0)	0	—[‡]	—[‡]
Naltrexone	2	1 (50.0)	37.39	—[‡]	—[‡]
Metronidazole	155	21 (13.5)	15.12	**1.55 (1.01–2.38)**	1.44 (0.94–2.22)

*The reference group included pregnancies not exposed to reactive intermediate-inducing drugs or drugs exhibiting folic acid antagonism.
[†]Used alone or in combination with other RI-inducing drugs; subcategories are not mutually exclusive.
[‡]The HRs were not calculated because of the possibility of statistical instability (fewer than five outcomes per predictor variable in the exposed group).
[§]CVD: cardiovascular drugs, including clopidogrel, amiodarone, spironolactone, propranolol, verapamil, diltiazem, captopril, and losartan.
[¶]NSAIDs: nonsteroidal anti-inflammatory drugs, including indomethacin, diclofenac, ibuprofen, and naproxen.
**AEDs: antiepileptics, including phenobarbital, primidone, phenytoin, carbamazepine, valproic acid, and lamotrigine.
[††]Phenobarbital and primidone were combined into one category because phenobarbital is a metabolite of primidone.
[‡‡]Antidepressants: including imipramine, clomipramine, amitriptyline, nortriptyline, mianserin, trazodone, nefazodone, and duloxetine.
[§§]NSRIs: non-selective monoamine reuptake inhibitors, including imipramine, clomipramine, amitriptyline, and nortriptyline.
HRs were adjusted for maternal age, diabetes, and the total number of medications taken by the pregnant woman.
CI, confidence interval.
Significant values are in bold.

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metabolism increases. This occurs concurrently with a brain growth spurt in mid-pregnancy, which means that an insult of environmental factors could cause widespread neuronal damage.[3] Another explanation for the increased HR with the second-trimester exposure is that our study used a live-born population. This might underestimate the risk with the first-trimester exposure, which could result in severe structural brain defects, leading to *in utero* deaths or pregnancy terminations.

Grouping 48 drugs according to their potential for RI induction, on one hand, increases the power to examine our hypothesis of RI-inducing mechanism. On the other hand, this raises an issue of heterogeneity because the association with psychotropics use in children could be driven by the dominant drug/drug class. However, when we examined 48 drugs individually, the results indicated an overall pattern of the increased HRs found with most RI-inducing drugs. In addition, the dose–response relationship showed an increased incident use of psychotropic medications among children who had prolonged exposure to RI-inducing drugs. This further strengthens our hypothesis of RI-inducing mechanism.

In consideration of the types of psychotropic medications used by the children, the significant association between prenatal exposure to RI-inducing drugs and the children's initiation of psychostimulants and antimigraine preparations suggests attention-deficit/hyperactivity disorder and migraine/headache, respectively, for which these drugs are most often prescribed.[20,21] However, it is noteworthy that there was a trend towards an increased use of other psychotropic medications as well. This suggests a possibly wide damage of RIs on the developing nervous system, as experimental studies previously observed.[2–4]

Strengths and limitations

Our study was based on a large prescription database that is representative of the Dutch population with a proven high accuracy and the possibility of tracking patients over time, even when the patients receive their medication from different pharmacies.[10,11] Therefore, the database is suitable for studies on developmental outcomes, which often require a large sample size and long follow-up time. Our data are not affected by recall bias because the exposure and outcome were recorded prospectively.

Our database has several limitations. Because there is no information about prescription indications, we could not easily translate the use of psychotropic medications into specific diseases. For example, the use of antipsychotics has been associated with various diseases.[22] In addition, because the database has incomplete information about OTC drugs, the exposure might have been underestimated if RI-inducing drugs, like diclofenac and paracetamol, had been used without a prescription. However, one study[23] has shown that 12.5% of pregnant women in the Netherlands use OTC medications and only 4.1% use analgesics. Therefore, incomplete information on OTC use is not expected to have a large influence on our finding. We were also unable to investigate the role of folic acid, which has been suggested to be protective in conditions of increased RI and ROS damage[24–26] because it may be used without a prescription. Another limitation is that we do not know whether the pregnant women actually used the drugs, probably leading to an overestimation of the exposure. However, the sensitivity analysis on pregnant women receiving at least two prescriptions of RI-inducing drugs confirmed our significant findings with RI+/FAA+ and RI+/FAA− in the first and second trimesters. Our standardized definition of pregnancy duration (273 days) may lead to some misclassification of exposure (i.e., an overestimation or underestimation of the exposure in each trimester), but we reduced it by excluding multiple-birth pregnancies, which are expected to have a shorter gestational duration.[27]

We used the pregnancy database that linked a mother to her child using an address code and the follow-up started from the child's birth date. However, because the IADB database only involved pharmacies in the Northern Netherlands, we did not have information of previous treatment of psychotropic medications (if any) if the child was born elsewhere and then moved to our region. Therefore, we did not include these children in the analyses and could not compare their medication profile with children that were linked to their mothers.

Although the database had no information about other risk factors (e.g., maternal smoking and alcohol use), this should not mitigate our findings because of the following: (1) we had a large study population that would ameliorate the problem of unequally distributed risk factors (if any); (2) we minimized other potential sources of RIs and ROS by adjusting for maternal age and diabetes[16,17]; (3) we limited the possibility of detection bias by adjusting for the total number of medications taken by the pregnant women; and finally, (4) we demonstrated a dose–response relationship of RI-inducing drugs and the incident use of psychotropic medications among children.

In conclusion, our study found a significant association between prenatal exposure to RI-inducing

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drugs and the children's initiation psychotropic medications (especially antimigraine preparations and psychostimulants). The pronounced association with the first-trimester and second-trimester exposure suggests an increased detrimental effect during critical periods of brain development.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Prenatal exposure to RI-inducing drugs is associated with the increased incident use of psychotropic medications among children.
- The association was more pronounced in pregnancies exposed to RI-inducing drugs during the first and second trimesters.
- Although the exposed children had a higher incident use of most psychotropic drugs, the association was significant for antimigraine preparations and psychostimulants after adjustment for potential confounders.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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