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ORIGINAL RESEARCH

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Use of signal detection methods to identify associations between prenatal medication exposure and subsequent childhood cancers: a Nordic hypothesis-generating registry-based study

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ABSTRACT

Background: Childhood cancer is an important contributor to childhood mortality in high-income countries. Information on associations between childhood cancer and in-utero exposure is absent or limited for most medications. Signal detection methods identify medications where research should be focused but have not been applied to datasets containing prenatal medication exposures and childhood cancers.

Research design and methods: The aim of this study was to apply and evaluate four signal detection methods – odds ratios (OR), the information component (IC), sequential probability ratio testing (SPRT), and Bayesian hierarchical models (BHM) – for identification of associations between medications dispensed during pregnancy and subsequent, incident diagnosis of childhood cancer <10 years, using linked Nordic registry data. Signal detection results were compared to propensity score adjusted odds ratios from generalized linear models.

Results: Analysis was performed for 117 medication-cancer pairs with 5 or more observations. The OR had the greatest sensitivity (0.75). The IC had a greater specificity (0.98) than the OR (0.95).

Conclusions: The IC may be the most appropriate method for identifying signals within this type of data. Reported signals should not be considered sufficient evidence of causal association and must be followed-up by tailored investigations that consider confounding by indication.

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Signal detection; childhood cancer; medication in pregnancy; prenatal exposure; pharmacovigilance; disproportionality analysis; Nordic registry data

1. Introduction

Childhood cancer is the second-leading cause of death for children aged 5–14 years in high-income countries [1]. Incidence rates among children aged 0–19 years vary across Europe, from approximately 120 to 230 per million per year, with most common malignancies being central nervous system neoplasms, leukemia's, and lymphomas [2].

The etiology of childhood cancer is thought to involve a combination of genetic [3] and environmental factors [4–6]. Possible carcinogenic environmental risk factors include exposures that cross the placenta during the early formation of organs [7]. Many pregnant women take prescribed or over-the-counter medication during their pregnancy [8], and as such medications are a common prenatal exposure.

Genotoxicity and carcinogenicity testings are mandatory for market authorization, however animal studies can have poor predictive value in humans [9]. Consequently, information on risk of carcinogenicity in humans is absent or limited for many medication exposures during pregnancy. Only a small number of studies have investigated associations between exposure to in-utero medication and subsequent childhood cancer [10]. Many of these have major limitations, including the use of composite outcomes and exposures; small sample sizes; observation periods that are too short; failure to control for confounders; and dependence upon self-reporting of medication use [10].

A safety signal is defined as any reported information on a possible causal relationship between a medication and adverse event, where the relationship was previously unknown or undocumented. Signal detection methods are quantitative statistical methods used to detect safety signals. They are commonly used within spontaneous adverse drug reaction reporting systems for pharmacovigilance. These methods analyze all possible associations between all medications and all adverse outcomes, identifying a small number of specific medication-outcome pairs where more individuals than expected by chance have both the exposure and outcome (signals). These signals cannot be taken as evidence of causal associations but require further investigation. Signal detection methods can help identify where research should be focused for the most impact. Such methods have been used to screen for medication-cancer signals in adults [11–14] but are yet

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to be applied to electronic health registries involving in-utero exposure and subsequent childhood cancers.

The aim of this study was to investigate the performance of four signal detection methods in identifying associations between medication use during pregnancy and subsequent childhood cancer risk, using nationwide health registries from three Nordic countries. We selected six large medication groups that are frequently used among women of childbearing age (antibiotics, antidiabetics, cardiovascular medications, immunosuppressive agents, sex hormones, and thyroid therapy), where previous studies have identified potential harmful associations between either the medication and childhood cancer [15–17], medication and adult cancers [18–20], or medication indication and childhood cancer [21–25].

As information on carcinogenicity of medications during pregnancy is limited, it is unknown which medications truly increase the risk of specific cancers. Propensity scores are a statistical technique that use the probability of being exposed conditional on a set of covariates. Individuals with the same propensity score have the same probability of being exposed given the set of covariates, and therefore the score can be used to control for any association between the exposure and confounding factors. As there is no gold-standard to compare detected signals to, we compared detected signals to the established method of propensity score adjusted odds ratios from generalized linear models. In general, calculating propensity score adjusted odds ratios for all medication-event combinations (typically hundreds or thousands of combinations) would be too time-consuming. However, in this study we had only a small number of medication-cancer combinations with enough observations for analysis which allowed us to use results from propensity score adjusted odds ratios as our reference-standard.

We additionally investigated the effect of introducing confounding control into the signal detection analysis pipeline, by using propensity scores to calculate standardized morbidity weights (SMW) to re-weight the populations prior to applying the signal detection methods.

2. Patients and methods

2.1. Study design

The design was a registry-based cohort study using health care data from Norway, Sweden, and Finland.

2.2. Data sources

Nationwide Nordic medical birth registry, prescription registry, cancer registry, and population registry data from Norway, Sweden, and Finland were used with linkage of data facilitated by unique personal identification numbers.

The Nordic medical birth registries provide accurate information on children eligible for inclusion. Notification has been mandatory for all livebirths since 1987 in Finland, 2007 in Norway, and 1973 in Sweden [26–28]. In Norway, date and cause of death, and date of migration, are also available within the medical birth registry. Population registries provide information on date and cause of death in Finland from 1997 [29], and Sweden from 1952 [30].

Prescription registries contain records of all prescription dispensing and reimbursement at pharmacies, including date of dispensing and the medication's Anatomical Therapeutic Chemical (ATC) code [27,31]. These registries have been available since 1994 in Finland, 2004 in Norway, and 2005 in Sweden [27,31].

Cancer registries contain information on cancer diagnosis. For childhood cancers, these are recorded using the International Classification of Diseases for Oncology (ICD-O-3) [32] and have been mapped to the International Classification of Childhood Cancer 3rd Edition (ICCC3) [33]. Reporting of incident cancers to the cancer registries has been mandatory since 1953 in Finland and Norway, and 1958 in Sweden [27,34]. Coverage varies between countries but is estimated to be over 90% for all [35–38].

2.3. Study population

The study population was all liveborn children recorded in the medical birth registries as born in the years 2007–2013 in Norway, 2010–2014 in Sweden, and 1997–2014 in Finland. Children were excluded if they, or their mother, had a missing identification number, as this would prevent linkage between registries. Children were also excluded if birthday or gestational age at birth were missing as this would prevent identification of the pregnancy window (Figure 1). Follow-up continued until cancer diagnosis or censoring due to death, emigration (only available for Norway), the child's 10th birthday or end of the study period 31 December 2019.

The total study population for analysis was 2,023,510. Analysis was performed overall (i.e. for ages 0–9 years, population 802,293), and stratified by ages 0–4 (population 1,952,263) and 5–9 (population 801,163), as peak age of incidence differs by cancer type (Figure 1). Note that the sample size for the age group 0–9 years is smaller than the sample size for ages 0–4. Analysis for 0–9 years and 5–9 years excluded children born after 2010, as they were born too late to complete 10 years follow-up. Complete follow-up was required for both adjusted and unadjusted analysis.

2.4. Exposures

Exposure was defined as one or more maternal prescriptions of either antibiotics (ATC codes starting with J01), antidiabetics (ATC codes starting with A10), cardiovascular medications (ATC codes starting with C), immunosuppressive agents (ATC codes starting with A07E, H02A, L04A or M01), sex hormones (ATC codes G02BB01 or G02BA03, or starting with G03) or thyroid therapy (ATC codes starting with H03), at the 4th level ATC code, recorded in the prescription registries. A full list of ATC codes can be found in Supplementary Tables S1a–S1f.

The exposure window was defined as dispensing of prescription during pregnancy, from pregnancy start (last menstrual period calculated from gestational age at birth) to birth, as recorded in the medical birth registries. The same exposure window was used for all investigated medications.

Non-exposed were defined as women who were not dispensed the medication of interest during their pregnancy.

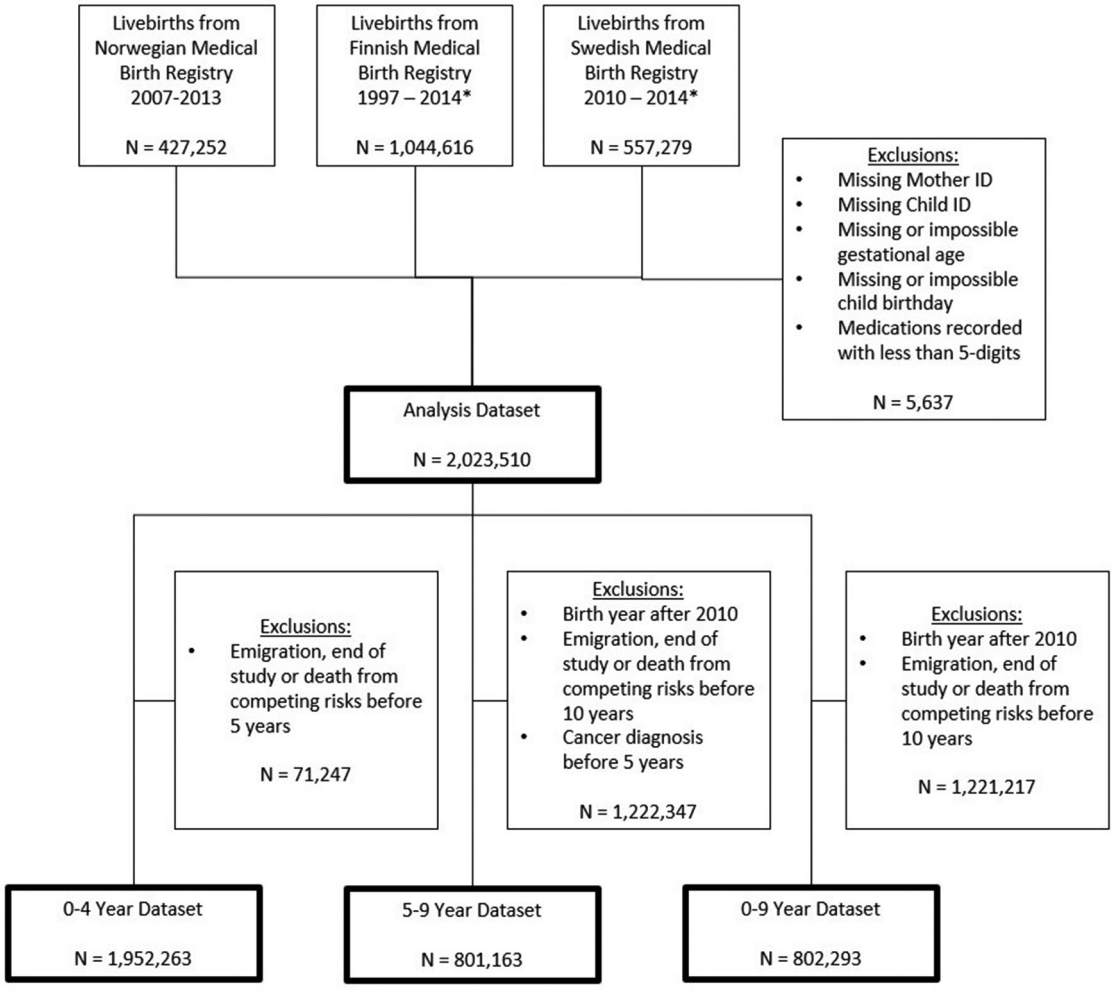

Figure 1. Flow-chart of study population.

Flowchart of the study population. * Individuals with missing identification number or gestational age were pre-excluded by registry holders, and information on the number excluded for this reason was not provided. The 2,023,510 individuals within the 'Analysis Dataset' were used to model propensity scores.

These women may have been dispensed other medications during their pregnancy.

2.5. Outcomes

Outcomes were defined as the first incident cancer diagnosed prior to the child's 10th birthday given by ICCC3 subgroups, as recorded in the cancer registries. A full list of ICCC3 subgroups can be found in Supplementary Table S2. Childhood cancers arise from embryonal tissues and so do not completely map to the traditional organ systems used for classifying adult cancers. The ICCC3 is based on the type and behavior of cancer cells and the most common childhood cancers have individual codes, making it preferable over ICD classification [33]. ICCC3 subgroups were analyzed individually and not grouped, as grouping of heterogenous cancers may reduce precision.

2.6. Covariates

As outcomes were expected to be rare, and many covariates were available, propensity score adjustment was chosen to account for imbalance in measured baseline characteristics and risk factors for the outcome between exposure groups [39].

Covariates for adjustment were chosen a priori using subject knowledge and Directed Graphs (Supplementary Figure S1).

The following covariates were included. From the medical birth registries: source country (Norway, Sweden, Finland); mother's age (categorical: <20, 20–24, 25–29, 30–34, 35–39, 40+); chronic hypertension (yes/no); chronic diabetes (yes/no); gestational diabetes for antidiabetic medications only (yes/no); centered calendar year at birth (indices); assisted reproductive technology (yes/no); child sex (male/female); parity (categorical: 0; 1; ≥2; missing); smoking in early pregnancy (categorical: yes; no; missing). From the cancer registries: history of maternal cancer prior to pregnancy (yes/no). From the prescription registries: medications dispensed to at least 100 women, and at least 10 women exposed to the medication and 10 women unexposed to the medication in the 3-months prior to pregnancy for individual 2nd level, 3rd level, and 4th level ATC codes (used as a proxy for comorbidities); any medication dispensed 3-months prior to pregnancy at any level of ATC (yes/no); number of different medications

dispensed at any level of ATC in the 3-months prior to pregnancy (indices). Gestational diabetes was included as a covariate for antidiabetic medications as it was considered a strong predictor of medication use in pregnancy. As a diagnosis of gestational diabetes may have occurred after the dispensation of non-antidiabetic medications, it was not included as a covariate for non-antidiabetic medications. Full details of covariate definitions and covariates used within each propensity score can be found in supplementary material (page 8–19).

2.7. Missing data

Cases with missing ID, gestational age or birth date were excluded from the analysis as described above. Cases with missing child sex (<5) were excluded from the propensity score analysis. There was no missing data in dispensing or diagnosis dates. A total of 1.1% of cases (21,855) were missing parity, and 5.7% of cases (114,998) were missing smoking in early pregnancy. No imputation was performed; missing was included as a category within the propensity score for parity and smoking variables.

2.8. Signal detection methods

Signal detection methods can indicate where a medication-cancer pair is occurring more frequently than may be expected by chance. Where these methods identify that a pair is occurring more frequently, this suggests a potential increased risk of cancer with the use of the medication. This is referred to below as a 'signal of harm.' The odds ratio (OR), information component (IC), sequential probability ratio testing (SPRT), and Bayesian hierarchical modeling (BHM) methods were investigated.

2.8.1. Odds ratio (OR)

For each $i = 1, \ldots I$ in-utero medications and $j = 1, \ldots J$ childhood cancers, the following 2-by-2 table (Table 1) can be defined:

The odds ratio for each medication-childhood cancer pair can be calculated with Equation 1.

$$OR_{ij} = \frac{(a_{ij} \div c_{ij})}{(b_{ij} \div d_{ij})} \tag{1}$$

A 95% confidence interval can be calculated using Equation 2.

$$e^{\log(OR_{ij}) \pm \left(1.96 \times \sqrt{\left(\frac{1}{a_{ij}}\right)+\left(\frac{1}{b_{ij}}\right)+\left(\frac{1}{c_{ij}}\right)+\left(\frac{1}{d_{ij}}\right)}\right)} \tag{2}$$

Table 1. 2-by-2 table frequencies for each medication-cancer pair.

	Exposed to *i* 4th level ATC medication of interest	Unexposed to 4th level ATC medication of interest
Incident *j* ICCC3 diagnosis of interest	a_{ij}	b_{ij}
No incident ICCC3 diagnosis of interest	c_{ij}	d_{ij}

A OR greater than 1 indicates the medication-cancer pair is occurring more frequently than expected by chance. This would suggest a potential increased risk of cancer with this medication. A signal of harm was defined as the lower limit of the 95% confidence interval exceeding 1.

2.8.2. Information component (IC)

The IC is a popular signal detection method [40] which uses Bayes theorem. For any individual pregnancy, there is a prior probability that the child may subsequently develop a specific childhood cancer $P(Cancer_j)$. There is also a prior probability that the child is exposed to a specific medication in utero $P(Medication_i)$.The probability of being both exposed and developing the cancer is known as the coincident probability $P(Cancer_j, Medication_i)$.

For each medication-cancer pair an information component (IC) can be calculated using the likelihood ratio from the observed numbers of exposures and cancers, an assumed distribution of the number of exposures and cancer, and an uninformative prior [40] (Equation 3).

$$IC_{ij} = \log_2\left(\frac{P(Cancer_j, Medication_i)}{P(Cancer_j) \times P(Medication_i)}\right) \tag{3}$$

An IC greater than 0 indicates the medication-cancer pair is co-occurring more frequently than expected, while an IC less than 0 indicates the pair is co-occurring less frequently than expected. The IC can be transformed onto the same scale as the risk ratio to aid interpretation. A signal of harm was defined as the lower limit of the 95% credible interval exceeding 0 (transformed 95% credible interval exceeding 1).

2.8.3. Sequential probability ratio testing (SPRT)

The SPRT is a relatively new method of signal detection that has primarily been used to scan electronic health records for vaccine studies [41]. Assuming observations can be described by a Poisson distribution, the log-likelihood ratio (LLR) can be defined using Equation 4.

$$LLR_{ij} = O_{ij} \times \log_e(hRR) - E_{ij} \times (hRR - 1) \tag{4}$$

Using the frequencies defined in Table 1, $O_{ij} = a_{ij}$, and E_{ij} is the expected number of diagnoses *j* when exposed to medication *i* under the assumption of independence, as calculated using Equation 5.

$$E_{ij} = \frac{(a_{ij} + c_{ij})(a_{ij} + b_{ij})}{(a_{ij} + c_{ij} + b_{ij} + d_{ij})} \tag{5}$$

The *hRR* is a hypothesized relative risk, which we specified as either 4 or 2, indicating a quadrupling or doubling of the risk. A threshold of 2.95 approximately corresponds to a theoretical type 1 error of 0.05 and a power of 0.95 [41]. A signal of harm was defined as an LLR greater than 2.95 for *hRR*of 4 or 2.

2.8.4. Bayesian hierarchical model (BHM)

Hierarchical models can incorporate the underlying grouped structure of the medications and cancers. Berry and Berry's hierarchical mixture model for the identification of adverse reactions within clinical trials [42] can be combined with the

assumption that each frequency count is drawn from a Poisson distribution as shown in Equation 6.

$$O_{ij}|\delta_{ij}\left(e^{\delta_{ij}}E_{ij}\right) where \delta_{ij} = \log\left(\frac{O_{ij}}{E_{ij}}\right) \quad (6)$$

A 2-dimentional Bayesian hierarchical model based on both drug and cancer groupings can then be defined through the definition of the hyperparameters for $m = 1, \ldots, M$ medication groups and $ca = 1, \ldots, CA$ cancer groups, as shown in Equation 7.

$$\delta_{ij}\left(\mu_{m_i ca_j}, \tau_{m_i ca_j}\right) where \tau_{m_i ca_j} = \frac{1}{\sigma^2_{m_i ca_j}} \quad (7)$$

We specified vague priors for these hyperparameters as $\mu_{m_i ca_j} \sim Norm(0, 0.05)$ and $\tau_{m_i ca_j} \sim Gamma(0.01, 0.01)$. A signal of harm was defined as a 95% credible interval for δ_{ij} exceeding 1 [42].

2.9. Statistical analysis

All analyses were performed using R version 4.2.2 [43]. Analysis was conducted on a combined dataset of all three countries stored at the University of Oslo on a secure server. Baseline characteristics were compared between children exposed to each type of medication.

OR, IC, SPRT and BHM statistics were calculated for each medication-cancer pair with at least 5 observations for the 0–9 years analysis, and the 0–4 and 5–9 years analysis, without any adjustment, and with weighting by propensity score. Model specifications, including groupings used within the BHM models, can be found in supplementary material (p. 7–8).

2.9.1. Calculation of reference associations

Propensity to each medication was calculated for all included individuals using generalized linear models with covariates listed above; logit links; and interaction terms between maternal age, source country, and centered birth year. Full details of model covariates can be found in supplementary material (page 8–19). Stürmer trimming was used to reduce bias from confounding in the tails of the distributions, with the lower cut-point the 2.5th percentile propensity score in the treated, and upper cut-point the 97.5th percentile propensity score in the untreated [44]. The balance of weights was checked using standardized mean differences [45]. Covariates were considered balanced if differences were <0.1 [45].

Generalised linear models were then used to calculate odds ratios for medication-cancer pairs with at least 5 observations following trimming for the 0–9 years, 0–4 years, and 5–9 years analysis. Model covariates included the medication of interest; propensity score for the medication of interest; and any variables that were still unbalanced following propensity score adjustment. Full details of model covariates can be found in supplementary material (page 19–20).

2.9.2. Confounding control within the signal detection pipeline with SMW

Each signal detection method was also applied to a re-weighted population, using SMW, with the aim of incorporating confounding control into the signal detection pipeline. SMW is preferred when the comparator group is untreated [46], answering the question: 'What would have happened if we had not exposed the treated to the treatment?' Individuals dispensed the medication of interest are given a weight of 1, while individuals not dispensed the medication are given a weight based on the modeled propensity to the medication, found in Equation 8.

$$SMWinuntreated = \frac{PS}{(1 - PS)} \quad (8)$$

2.9.3. Signal detection performance

Four properties of the signal detection methods were calculated assuming all statistically significant (at the 5% level) propensity score adjusted odds ratios indicated true associations (the reference standard). True positive (TP); True negative (TN); False positive (FP) and False negative (FN) signals were determined as defined in Table S3.

Sensitivity is the proportion of pairs identified as signals of harm, where the propensity score adjusted odds ratio was statistically significant at the 5% level (Equation 9).

$$Sensitivity = \frac{TP}{TP + FN} \quad (9)$$

Specificity is the proportion of pairs not identified as signals of harm where the propensity score adjusted odds ratio was not statistically significant at the 5% level (Equation 10).

$$Specificity = \frac{TN}{TN + FP} \quad (10)$$

Positive predictive value is the probability that an identified signal of harm has a propensity score adjusted odds ratio that is statistically significant at the 5% level (Equation 11).

$$Positive\ Predictive\ Value = \frac{TP}{TP + FP} \quad (11)$$

Negative predictive value is the probability that a pair not identified as a signal of harm does not have a propensity score adjusted odds ratio that is statistically significant at the 5% level (Equation 12).

$$Negative\ Predictive\ Value = \frac{TN}{TN + FN} \quad (12)$$

3. Results

The initial combined dataset included 2,023,510 children with 3,435 cancers (0.17%) diagnosed before the age of 10. The most common cancer was lymphoid leukemia (993 children, 29%), followed by astrocytoma (304 children, 8.9%), and neuroblastoma and ganglioneuroblastoma (265, 7.7%).

In total, 701,743 children (35%) had mothers who fulfilled prescriptions for at least one antibiotic, antidiabetic, cardiovascular medication, immunosuppressive agent, sex hormone,

or thyroid therapy during the pregnancy window. The most dispensed medications were J01CA Penicillins with extended spectrum (258,418 pregnancies, 13%), J01CE Beta-lactamase sensitive penicillins (121,532 pregnancies, 6.0%), and J01DB First generation cephalosporins (109,932 pregnancies, 5.4%). In total, 223,662 mothers (11%) had more than one prescription of a medication of interest during the pregnancy window.

In total, 1,952,263 children (96%) were included in the 0–4 analysis; of which 2,429 (0.12%) were diagnosed with cancer within the first 5 years of life. Furthermore, 802,293 children (40%) were included in the 0–9 analysis, and 801,163 (40%) in the 5–9 analysis (1,221,217 children (60%) were excluded due to being born after 2010, too late to have 10 years follow-up before the study end date); of which 1,762 (0.22%) were diagnosed with cancer in the first 10 years of life, and 632 (0.08%) were diagnosed between the ages of 5 and 9 years (Figure 1).

The proportion of pregnancies exposed differed between the six medication groups (25% exposed to antibiotics; 4.6% exposed to sex hormones; 3.7% exposed to immunosuppressive agents; 3.3% exposed to thyroid therapy; 2.8% exposed to cardiovascular medications; and 1.5% exposed to antidiabetics). Differences in characteristics between non-exposed and those dispensed one or more of the six medication groups investigated were as expected for each medication group (Table 2). For example, 46% of individuals dispensed antidiabetics had gestational diabetes compared to 4.8% in those unexposed to any medication group of interest; 50% of those dispensed sex hormones used assisted reproductive technology compared to 3.8% in those unexposed.

3.1. Results of signal detection

Signal detection methods were only calculated for medication-cancer pairs, with at least 5 observations: 67 medication-cancer pairs within the 0–4 years analysis; 11 pairs within the 5–9 years analysis; and 39 within the 0–9 years analysis. A total of 17 medication groups had at least one pair included in the analysis (identified in Supplementary Table S1a–S1f). Full results for these can be found in Supplementary Tables (S4–S73).

3.2. Performance according to reference associations

Propensity scores were calculated for each medication included in the analysis. For 11 of the 17 medication groups, all important covariates (source country; maternal age; chronic hypertension; chronic diabetes; assisted reproductive technology; smoking; parity; child sex; and maternal cancer prior to pregnancy) were balanced following adjustment. Medications that continued to have some unbalanced covariates following adjustment were fast, intermediate, and long-acting insulins and analogues for injection; alpha and beta blocking agents; pregen (4) derivatives; and gonadotropins. Density plots and balance are detailed in Supplementary Figures S2–S18.

Trimming of propensity score tails reduced the number of cancer observations within the exposed population, in some cases to below 5. The number of original and trimmed observations for each medication-cancer pair can be found in Supplementary Tables S4–S73. This could be attributed to large reductions in the population sizes for some medications with the use of Stürmer trimming cutoffs. For example, with fast, intermediate, and long-acting insulins and analogues for injection, trimming removed 88%, 72% and 95% of the dispensed population, respectively. Other medications with large reductions in the dispensed population included pregen (4) derivatives (79%); and gonadotrophins (86%).

As the trimmed populations were unlikely to be representative of the population of women dispensed these medications, generalized linear regression modeling with propensity score adjustment was only calculated for medication-cancer pairs with at least 5 observations following trimming (48 pairs within the 0–4 analysis; 11 pairs within the 5–9 analysis; 28 pairs within the 0–9 analysis). There were increased odds at the 5% level for 4 medication-cancer pairs (8.3%) with at least 5 observations following trimming in the 0–4 year analysis; 1 medication cancer pair (10%) in the 5–9 year analysis; and 3 medication-cancer pairs in the 0–9 year analysis (11%). Full results from these propensity score adjusted models can be found in Supplementary Tables S4–S73.

Results of the generalized linear regression modeling with propensity score adjustment were considered the reference standard for calculating sensitivity, specificity, positive predictive value, and negative predictive value of the four signal detection methods (Table 3). In the 0–4 analysis the OR had the highest sensitivity (0.75) identifying the most true positives ($n = 3$). The IC had a higher specificity (0.98) than the OR (0.95), identifying fewer false positives (1 and 2 respectively). The SPRT identified one true positive, while the BHM failed to identify any true positives in the 0–4 analysis.

Signal detection results for the 8 medication-cancer pairs with increased adjusted odds at the 5% level are presented in Figure 2. The only pair not identified by any signal detection method (a false negative) was lymphoid leukemia with the use of Beta-lactamase resistant penicillins (adjusted odds ratio 2.8 (95% confidence interval 1.3–6.4)). True positive signals were all for CNS and peripheral nervous cell tumors.

The 3 medication-cancer pairs with false-positive signals are presented in Figure 3. The OR for neuroblastoma and ganglioneuroblastoma with propionic acid derivatives (2.1) was similar to the adjusted odds ratio (2.0), but with tighter confidence intervals (Figure 3(b)). Whereas the adjusted point estimates for retinoblastoma with first-generation cephalosporins (Figure 3(a)); and lymphoid leukemia with nitrofuran derivatives (Figure 3(c)) were somewhat lower than point estimates for the signal detection methods.

3.3. Signal detection with Re-weighting by SMW

Signal detection methods were also applied to the population re-weighted by SMW. Figure 4 demonstrates the pattern of results found for neuroblastoma and ganglioneuroblastoma with penicillins for extended spectrum, which is similar across the other medication-cancer pairs. Most OR point estimates were closer to the propensity score adjusted odds ratios after re-weighting. However, OR confidence intervals were wider; and IC and BHM point estimates and confidence intervals were shrunk toward the null. As such, only one signal was found following adjustment. Full results of

Table 2. Descriptive statistics of the study population by exposure.

Characteristics		Total Dataset		Exposed to J01: Antibiotics		Exposed to A10: Antidiabetics		Exposed to C: Cardiovascular Medications		Exposed to A07E, H02A, L04A or M01: Immunosuppressive Agents		Exposed to G02BB01, G02BB02 or G03: Sex Hormones		Exposed to H03: Thyroid Therapy	
Total, N		2,023,510		506,450		31,079		56,322		75,007		93,998		68,045	
Source Country	Norway, N (%)	421,639	(21)	119,694	(24)	5,572	(18)	11,896	(21)	13,493	(18)	28,148	(30)	11,070	(16)
	Finland, N (%)	1,044,616	(52)	270,303	(53)	19,159	(62)	27,150	(48)	44,520	(59)	37,344	(40)	24,602	(36)
	Sweden, N (%)	557,255	(28)	116,453	(23)	6,348	(20)	17,276	(31)	16,994	(23)	28,506	(30)	32,373	(48)
Mother Age Years, Mean (SD)		30	(5.3)	30	(5.5)	32	(5.5)	32	(5.5)	31	(5.6)	32	(5.5)	32	(5.2)
Chronic Hypertension, N (%)		14,416	(0.71)	4,475	(0.88)	1,397	(4.5)	6,018	(11)	1,053	(1.4)	868	(0.92)	997	(1.5)
Chronic Diabetes, N (%)		13,698	(0.68)	4,791	(0.95)	11,613	(37)	1,416	(2.5)	870	(1.2)	761	(0.81)	2,187	(3.2)
Gestational Diabetes, N (%)		97,669	(4.8)	29,615	(5.8)	14,410	(46)	3,694	(6.6)	5,816	(7.8)	5,075	(5.4)	5,103	(7.5)
Gestational Hypertension, N (%)		30,729	(1.5)	8,571	(1.7)	1,011	(3.3)	3,235	(5.7)	1,521	(2.0)	1,911	(2.0)	1,554	(2.3)
Preeclampsia, N (%)		45,603	(2.3)	12,166	(2.4)	2,221	(7.1)	5,050	(9.0)	2,260	(3.0)	4,292	(4.6)	2,492	(3.7)
Multiple Pregnancy, N (%)		60,844	(3.0)	15,605	(3.1)	1,291	(4.2)	2,909	(5.2)	2,902	(3.9)	13,602	(15)	2,657	(3.9)
Parity	0, N (%)	880,171	(44)	200,020	(40)	12,206	(39)	23,527	(42)	32,787	(44)	56,390	(60)	28,371	(42)
	1, N (%)	730,378	(36)	191,490	(38)	10,994	(35)	19,559	(35)	25,178	(34)	27,879	(30)	24,750	(37)
	≥2, N (%)	456,671	(23)	127,608	(25)	9,055	(29)	14,636	(26)	19,152	(26)	10,279	(11)	16,316	(24)
	Missing, N (%)	21,855	(1.1)	6,334	(1.3)	588	(1.9)	700	(1.2)	1,055	(1.4)	275	(0.29)	696	(1.0)
Assisted Reproductive Technology, N (%)		76,930	(3.8)	18,131	(3.6)	2,335	(7.5)	3,345	(5.9)	4,381	(5.8)	47,211	(50)	6,505	(9.6)
Smoking	Y, N (%)	343,863	(17)	102,477	(20)	5,646	(18)	9,300	(17)	15,798	(21)	11,527	(12)	8,403	(12)
	Missing, N (%)	114,998	(5.7)	29,425	(5.8)	1,553	(5.0)	3,183	(5.7)	3,828	(5.1)	5,894	(6.3)	3,604	(5.3)
Gestational Age Days, Median (IQR)		280	(273–286)	280	(272–286)	271	(263–279)	276	(268–284)	279	(271–285)	277	(268–285)	279	(271–286)
Preterm Birth, N (%)		113,537	(5.6)	29,993	(5.9)	4,816	(16)	7,075	(13)	5,981	(8.0)	12,222	(13)	4,858	(7.1)
Child Sex Male, N (%)		1,036,662	(51)	258,925	(51)	16,120	(52)	29,151	(52)	38,521	(51)	48,456	(52)	35,149	(52)
Birth Weight Grams, Mean (SD)		3,506	(578)	3,507	(583)	3,606	(693)	3,334	(705)	3,439	(615)	3,321	(702)	3,503	(618)
Birth Weight Missing, N (%)		2,052	(0.10)	434	(0.09)	29	(0.09)	48	(0.09)	83	(0.11)	111	(0.12)	53	(0.08)
Maternal Cancer	Before, N (%)	13,753	(0.68)	3,518	(0.69)	238	(0.77)	555	(0.99)	670	(0.89)	1,110	(1.2)	2,216	(3.3)
	During, N (%)	775	(0.04)	240	(0.05)	16	(0.05)	34	(0.06)	77	(0.10)	46	(0.05)	63	(0.09)
	After, N (%)	46,067	(2.3)	11,799	(2.3)	674	(2.2)	1,611	(2.9)	1,946	(2.6)	2,746	(2.9)	1,502	(2.2)

N, number; SD, standard deviation; IQR, interquartile range. *Less than 5 children had missing sex at birth.

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of unweighted signal detection methods.

Method	True Positives	False Positives	True Negatives	False Negatives	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
0–4 Year Analysis (48 pairs)								
OR	3	2	42	1	0.75	0.95	0.60	0.98
IC	2	1	43	2	0.50	0.98	0.67	0.96
SPRT	1	0	44	3	0.25	1.00	1.00	0.94
BHM	0	1	43	4	0	0.98	–	0.91
5–9 Year Analysis (11 pairs)								
OR	1	0	10	0	1.00	1.00	1.00	1.00
IC	1	0	10	0	1.00	1.00	1.00	1.00
SPRT	0	0	10	1	0	1.00	–	0.91
BHM	0	0	10	1	0	1.00	–	0.91
0–9 Year Analysis (28 pairs)								
OR	3	1	24	0	1.00	0.96	0.75	1.00
IC	3	1	24	0	1.00	0.96	0.75	1.00
SPRT	0	0	25	3	0	1.00	-	0.89
BHM	1	1	24	2	0.33	0.96	0.50	0.92

Positive Predictive Value is incalculable where no signals are identified (denoted by "–").

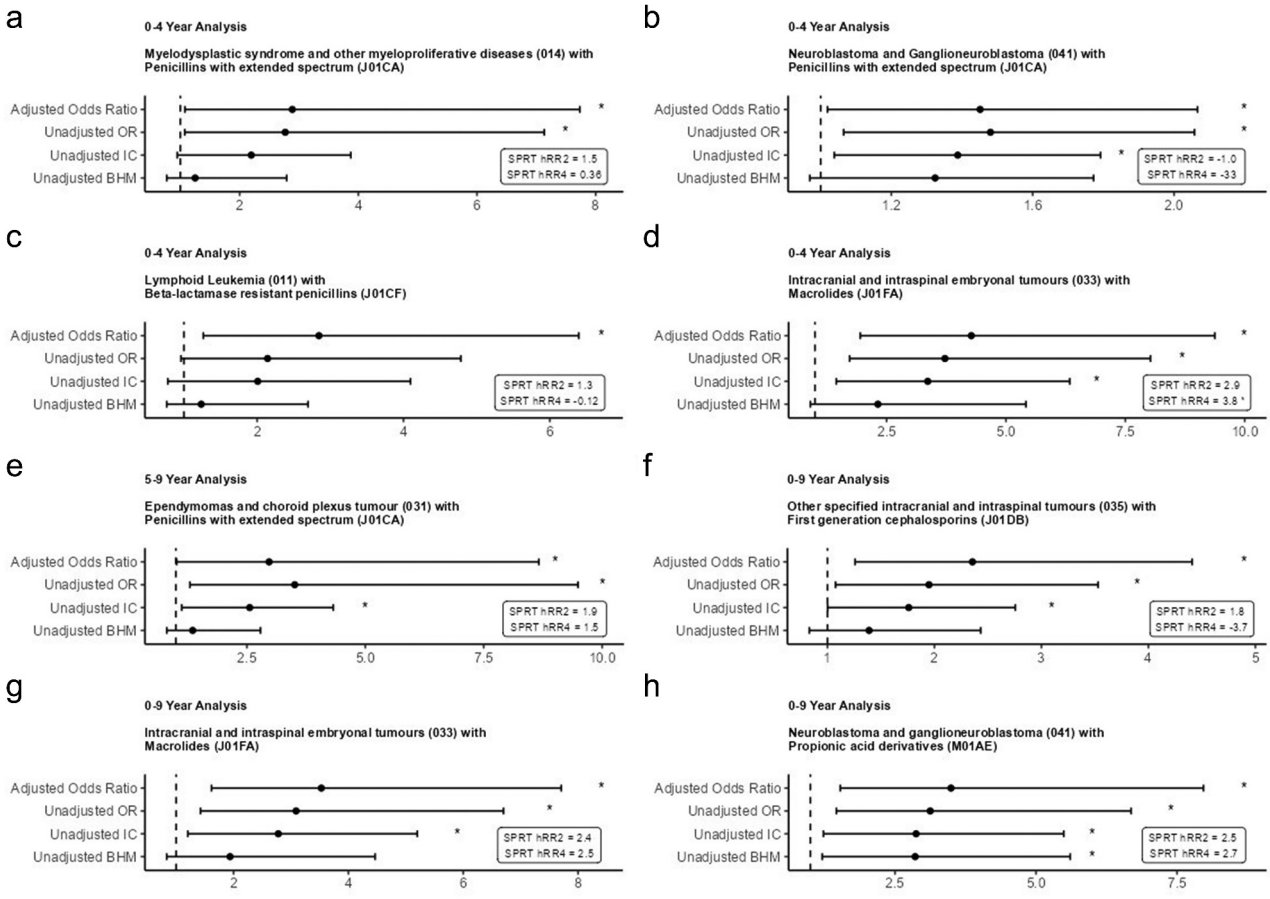

Figure 2. Unadjusted OR, IC, BHM and SPRT results for medication-cancer pairs with statistically significant increase in adjusted odds ratio.

Comparison of results from unadjusted OR, IC, BHM, SPRT, and adjusted odds ratios for pairs with an increased adjusted odds ratio at the 5% level. Odds ratios were adjusted for propensity score and additional covariates as needed. SPRT hRR2 uses a hypothesized relative risk of 2. SPRT hRR4 uses a hypothesized relative risk of 4. Dotted vertical line represents the null value of 1. BHM results have been transformed to the same scale as the OR, BHM, and Odds Ratio. Statistical significance/signal denoted by *.

propensity score weighted signal detection can be found in Supplementary Tables S4–S73.

4. Discussion

The most important findings of this study were that the traditional signal detection methods (OR and IC), without adjustment, can be used to identify areas to focus research on trans-generational carcinogenic associations. The use of the OR or IC should provide adequate power to detect signals requiring further investigation, while the use of the IC may help minimize false-positive signals. The SPRT and BHM models were unable to find signals within this dataset. These results are consistent with the known characteristics of the

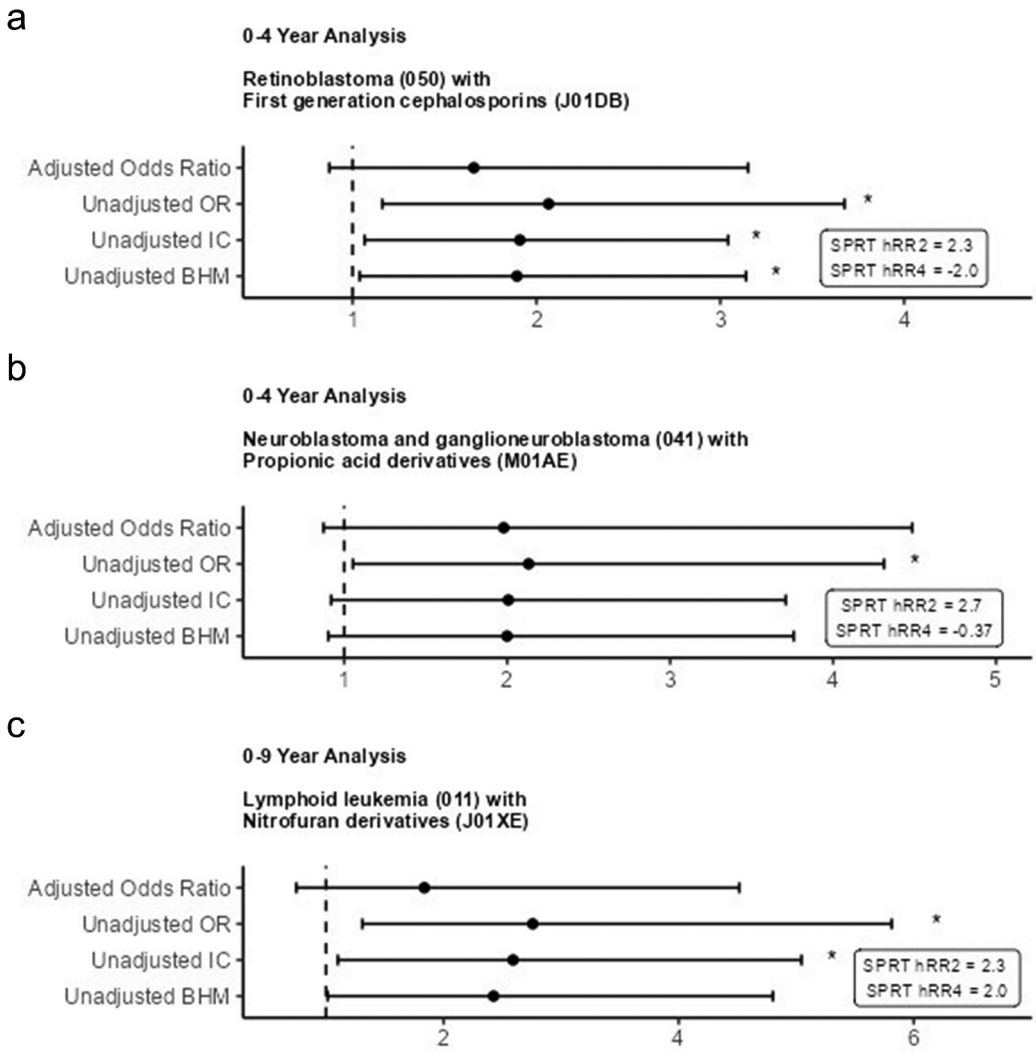

Figure 3. Medication-cancer pairs with false-positive signals from unadjusted OR, IC or BHM.

Comparison of results from unadjusted OR, IC, BHM, SPRT, and adjusted odds ratios for pairs with an identified signal, but adjusted odds ratio not significantly increased at the 5% level. Odds ratios were adjusted for propensity score and additional covariates as needed. SPRT hRR2 uses a hypothesized relative risk of 2. SPRT hRR4 uses a hypothesized relative risk of 4. Dotted vertical line represents the null value of 1. BHM results have been transformed to the same scale as the OR, BHM, and Odds Ratio. Statistical significance/signal denoted by *.

methods investigated when observed frequencies are low [47,48].

These findings are important as there has been little research in this area to date. Information on carcinogenic safety for the offspring for many medications used during pregnancy is lacking. Pharmacovigilance activities specifically tailored to address this knowledge gap are therefore warranted. Appropriate direction of research focus will help provide valuable information on potential harm and safety of medications.

Propensity score adjustment had several challenges in this setting, both for producing adjusted odds ratios, and for producing SMR re-weighted populations for signal detection. Calculated propensities were typically very small, due to the low proportions of women dispensed the specific medication, and most covariates not being strong predictors of medication use. For most medications, stronger predictions of medication use (e.g. infection during pregnancy for anti-infectives) were not available. Stürmer trimming was chosen as the preferred trimming strategy as it has been shown to reduce bias from unmeasured confounding with SMW weighting in simulations [49], however for the antidiabetic and hormonal medications this resulted in large reductions in the analysis population. Strong confounders for these medications were also highly predictive of medication use (i.e. diabetes for antidiabetics; and assisted reproductive technology for hormonal medications), resulting in poor overlap. Removal of these covariates may have improved overlap but would have left bias from strong residual confounding.

When applying signal detection methods to the re-weighted population, confidence intervals of the OR were wider and point estimates and confidence intervals of the IC and BHM were shrunk toward the null value. These effects are due to the reduction in population size, due to both trimming (reducing the actual size of the dispensed and control populations), and SMR weighting (reducing the effective size of the control population). As such, power to detect possible harm was reduced. Methods for re-sizing the population to be similar to that of the original population need to be investigated before propensity score adjustment can be incorporated into these signal detection methods.

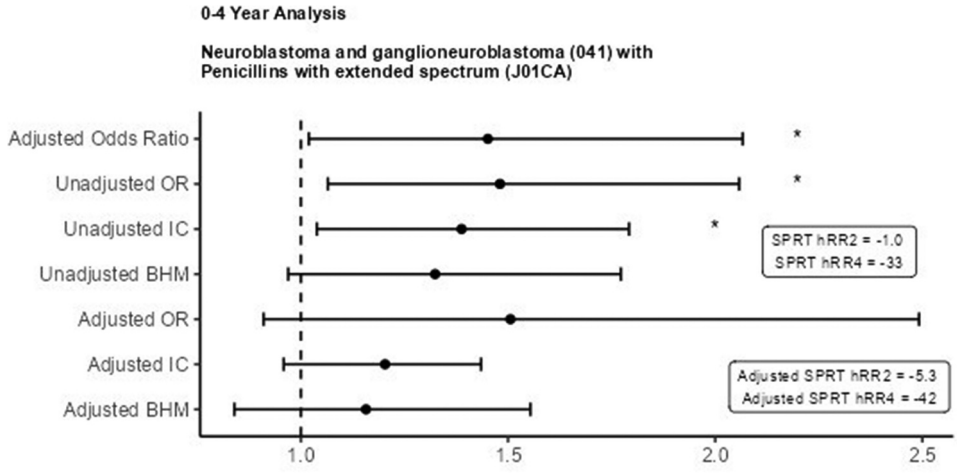

Figure 4. Adjusted and unadjusted OR, IC, BHM and GLM for J01CA–041.

Comparison of results from adjusted and unadjusted OR, IC, BHM, SPRT, and adjusted odds ratios for neuroblastoma and ganglioneuroblastoma with the use of penicillins with extended spectrum. Odds ratio was adjusted for propensity score. SPRT hRR2 uses a hypothesized relative risk of 2. SPRT hRR4 uses a hypothesized relative risk of 4. Dotted vertical line represents the null value of 1. BHM results have been transformed to the same scale as the OR, BHM, and Odds Ratio. Statistical significance/signal denoted by *.

There are several limitations to this study that should be acknowledged.

Firstly, medications were grouped to within the 4th level ATC code. Some of these medications have different properties with regard to ability to cross the placenta and possible biological plausibility for carcinogenicity. By grouping in this way, associations will be averaged across the group, potentially masking signals. However, due to the rarity of both the outcomes and exposures, this grouping was necessary to obtain a small number of meaningful results.

Secondly, several design choices will have introduced, and failed to account for, bias and confounding. Some misclassification of exposure is expected as the prescription registry does not provide information on medications dispensed in hospitals or confirm that a dispensed medication has been consumed (i.e. non-adherence). The definition of the exposure window may result in missing prescriptions that are infrequently fulfilled such as some contraceptives, however extending the window to prescription fulfilled in the months prior to pregnancy may result in inclusion of medications that were not taken during pregnancy. As prescriptions are recorded prospectively and irrespective of the cancer outcome, any such misclassification of exposure is expected to be non-differential and drive bias toward the null.

Propensity score adjustment was restricted to the variables available within the registry datasets. The use of alternative covariates may have improved the balance. A single propensity score was used for pooled data with the inclusion of a variable for the source county. Specifying individual propensity scores for each country may have improved model performance but would also have increased complexity and computation time. Missing variables were included as a category for parity and smoking, rather than imputed. Maternal cancer was used as a variable but could have alternatively been used as an exclusion criterion. However, as the outcome was rare, a choice was made to minimize exclusions.

We used propensity score adjusted odds ratios as the reference standard for calculating performance metrics of the signal detection methods investigated. It is important to note that this was used as a 'best available' standard, and medication-cancer pairs with increased odds may not be indicative of causal associations. We also did not adjust for multiple comparisons, and as such 5% of identified associations can be expected to have arisen by chance. Most identified associations are for pairs that are yet to be thoroughly researched such as CNS and peripheral nervous cell tumors with macrolides, first generation cephalosporins, and propionic acid derivatives. Further investigation of the associations identified here are required that consider covariates and exposure windows specific to the individual medications, and confounding by indication.

Sensitivity, specificity, positive predictive value, and negative predictive value were only calculated for pairs with at least 5 observations following trimming. The excluded pairs were more commonly for medications that had a greater imbalance prior to adjustment (e.g. at least one covariate with an SD > 1.0). As such, our conclusion that signal detection methods can identify areas of further study without the need for adjustment, is unlikely to extend to medications with large imbalances in important confounders.

5. Conclusions

Our results demonstrate that signal detection methods can be employed to identify associations between in-utero medication exposures and childhood cancers. These could potentially be used to screen for carcinogenic effects of medications used during pregnancy.

We recommend signal detection methods are used as a screening tool for in-utero medication-cancer associations and applied to a wider range of medication groups, including psychotropics, and antineoplastic agents. The IC or OR should be used as preferred methods due to the small observed frequencies. Further work is needed on the incorporation of propensity score adjustment within these signal detection methods, as it may further improve the sensitivity and specificity of these methods. For now, unadjusted signal detection should be performed, followed with consideration of the covariates for identified signals. Priority should be given to signals

with the largest point estimates identified by the adjusted analysis, largest observed frequencies, and a biologically plausible mechanism of carcinogenicity. Signals where the observed frequency is low should be followed-up with caution as they are more likely to be false positives.

Signals should not be considered as evidence of either harm or non-harm. All signals should be followed up by well-conducted causal observational studies that consider covariates specific to the individual medication and confounding by indication. Signals identified in this work are being investigated further by the Nordic Childhood Cancer Project.

We also recommend collaboration between countries where mother-child linkage to cancer registry data is feasible. Only with larger sample sizes and long follow-up time can these rare medication-childhood cancer associations be thoroughly investigated.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Regional Committee for Medical Research Ethics in South-Eastern Norway (approval number: 2018/142/REK Sør-Øst) and by the Swedish Ethical Review Authority [approval number: 2018/2604–31/1 2019–00268 (2019–02311)]. In Finland, registry-based studies are exempt from ethical review. The study was approved by local data-protection officers (approval numbers, Finland: THL/1179/6.02.00/2021, THL/2297/5.05.00/2018, Kela 120/522/2019, TK-53–1405-19; approval number, Norway: 233835). Data were handled in accordance with the research approvals and the applied legal norms, including the European Union General Data Protection Regulation (2016/79).

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Disclaimer

Data from the Cancer Registry of Norway (CRN) has been used in this publication. The interpretation and reporting of this data are the sole responsibility of the authors, and no endorsement by CRN is intended nor should it be inferred.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Data availability statement

Restrictions apply to the availability of these data, which were used under license for this study. Data are available to other researchers from the registry holders in Norway (https://www.fhi.no/en/overview/healthregistries/), Sweden (https://www.socialstyrelsen.se/en/statistics-and-data/registers/), and Finland (https://www.findata.fi) Access requires approval by ethical committees and/or data protection officers in each country.

Author contributions

Conceptualization (Johnson, Hannah. Morris, Joan. Nordeng, Hedvig); Methodology (Johnson, Hannah. Hjorth, Sarah. Nordeng, Hedvig. Morris, Joan. Pottegård Anton.); Formal analysis and investigation (Johnson, Hannah.); Writing – original draft preparation (Johnson, Hannah); Writing – review and editing (Johnson, Hannah. Hjorth, Sarah. Morris, Joan. Leinonen, Maarit. Norby, Ulrika. Nordeng, Hedvig. Pottegård Anton.); Funding acquisition (Nordeng, Hedvig); Supervision (Hjorth, Sarah. Morris, Joan, Nordeng, Hedvig); Data provision (Leinonen, Maarit. Norby, Ulrika. Nordeng, Hedvig).

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References

1. World Health Organisation. Global health estimates 2019: deaths by cause, age, sex, by country and by region, 2000–2019. Geneva: World Health Organisation; 2020.
2. Steliarova-Foucher E, Colmorn LB, Ries L, et al. International incidence of childhood cancer, volume iii (electronic version) lyon, France: international agency for research on cancer. [updated 2017 Apr 11; cited 2022 Oct 10]. Available from: http://iicc.iarc.fr/results/
3. Hanington L, Walker L, Wilson S. Paediatric cancer predisposition syndromes in the genomic age. Paediatr Child Health. 2022;32(5):184–190. doi: 10.1016/j.paed.2022.02.003
4. French AE, Grant R, Weitzman S, et al. Folic acid food fortification is associated with a decline in neuroblastoma. Clin Pharmacol Ther. 2003 Sep;74(3):288–294. doi: 10.1016/S0009-9236(03)00200-5
5. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer. 2006 Mar;6(3):193–203. doi: 10.1038/nrc1816
6. Greaves M. A causal mechanism for childhood acute lymphoblastic leukemia. Nat Rev Cancer. 2018;18(8):471–484. doi: 10.1038/s41568-018-0015-6
7. Fucic A, Guszak V, Mantovani A. Transplacental exposure to environmental carcinogens: association with childhood cancer risks and the role of modulating factors. Reprod Toxicol. 2017 Sep;72:182–190. doi: 10.1016/j.reprotox.2017.06.044
8. Haas DM, Marsh DJ, Dang DT, et al. Prescription and other medication use in pregnancy. Obstet Gynecol. 2018;131(5):789–798. doi: 10.1097/AOG.0000000000002579

9. SCHER/SCCP/SCENIHR. Risk assessment methodologies and approaches for mutagenic and carcinogenic substances. Brussels, Belgium: European Commission; 2008.
10. Hjorth S, Hemmingsen CH, Benevent J, et al. Maternal medication use and childhood cancer in offspring—systematic review and considerations for researchers. Am J Epidemiol. 2021 Nov 2;190 (11):2487–2499. doi: 10.1093/aje/kwab154
11. Kristensen KB, Friis S, Lund LC, et al. Identification of drug–cancer associations: a nationwide screening study. Cancer Res Commun. 2022 Jun;2(6):552–560. doi: 10.1158/2767-9764.CRC-22-0026
12. Pottegard A, Friis S, Christensen R, et al. Identification of associations between prescribed medications and cancer: a nationwide screening study. EBioMedicine. 2016 May;7:73–79. doi: 10.1016/j.ebiom.2016.03.018
13. Stoer NC, Botteri E, Thoresen GH, et al. Drug use and cancer risk: a drug-wide association study (dwas) in norway. Cancer Epidemiol Biomarkers Prev. 2021 Apr;30(4):682–689. doi: 10.1158/1055-9965.EPI-20-1028
14. McDowell RD, Hughes C, Murchie P, et al. A systematic assessment of the association between frequently prescribed medicines and the risk of common cancers: a series of nested case-control studies. BMC Med. 2021 Jan 26;19(1):22. doi: 10.1186/s12916-020-01891-5
15. Momen NC, Olsen J, Gissler M, et al. Exposure to systemic antibacterial medications during pregnancy and risk of childhood cancer. Pharmacoepidemiol Drug Saf. 2015 Aug;24(8):821–829. doi: 10.1002/pds.3806
16. Wainstock T, Walfisch A, Shoham-Vardi I, et al. Fertility treatments and pediatric neoplasms of the offspring: results of a population-based cohort with a median follow-up of 10 years. Am J Obstet Gynecol. 2017 Mar;216(3):e314 1–e314 14. doi: 10.1016/j.ajog.2017.01.015
17. Hargreave M, Morch LS, Andersen KK, et al. Maternal use of hormonal contraception and risk of childhood leukaemia: a nationwide, population-based cohort study. Lancet Oncol. 2018 Oct;19 (10):1307–1314. doi: 10.1016/S1470-2045(18)30479-0
18. Hicks BM, Filion KB, Yin H, et al. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study. BMJ. 2018 Oct 24;363:k4209. doi: 10.1136/bmj.k4209
19. Ocampo NV, Tafreshi J, Hauschild CL, et al. Cardiovascular medications and risk of cancer. Am J Cardiol. 2011 Oct 1;108(7):1045–1051. doi: 10.1016/j.amjcard.2011.05.041
20. Liu YC, Yeh CT, Lin KH. Molecular functions of thyroid hormone signaling in regulation of cancer progression and anti-apoptosis. Int J Mol Sci. 2019 Oct 9;20(20):4986. doi: 10.3390/ijms20204986
21. Contreras ZA, Ritz B, Virk J, et al. Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in california. Cancer Causes Control. 2016 Oct;27(10):1273–1285. doi: 10.1007/s10552-016-0807-5
22. Ekstrom K, Hjalgrim H, Brandt L, et al. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum. 2003 Apr;48(4):963–970. doi: 10.1002/art.10939
23. Seppala LK, Madanat-Harjuoja LM, Leinonen MK, et al. Maternal thyroid disease and the risk of childhood cancer in the offspring. Cancers (Basel). 2021 Oct 28;13(21):5409. doi: 10.3390/cancers13215409
24. Seppala LK, Madanat-Harjuoja LM, Troisi R, et al. Maternal autoimmune disease is not associated with cancer in the offspring. Acta Paediatr. 2021 Jul;110(7):2259–2266. doi: 10.1111/apa.15821
25. Seppala LK, Vettenranta K, Pitkaniemi J, et al. Maternal diabetes and risk of childhood cancer in the offspring. Int J Cancer. 2020 Aug 1;147(3):662–668. doi: 10.1002/ijc.32757
26. Langhoff-Roos J, Krebs L, Klungsoyr K, et al. The Nordic medical birth registers–a potential goldmine for clinical research. Acta Obstet Gynecol Scand. 2014 Feb;93(2):132–137. doi: 10.1111/aogs.12302
27. Laugesen K, Ludvigsson JF, Schmidt M, et al. Nordic health registry-based research: a review of health care systems and key registries. Clin Epidemiol. 2021;13:533–554. doi: 10.2147/CLEP.S314959
28. Cnattingius S, Kallen K, Sandstrom A, et al. The Swedish medical birth register during five decades: documentation of the content and quality of the register. Eur J Epidemiol. 2023 Jan;38(1):109–120. doi: 10.1007/s10654-022-00947-5
29. Official Statistics Finalnd (OSF). Official statistics of finland. 2023 [cited 2023]. Available from: https://www.stat.fi/meta/svt/index_en.html
30. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. Eur J Epidemiol. 2017 Sep;32(9):765–773. doi: 10.1007/s10654-017-0316-1
31. Furu K, Wettermark B, Andersen M, et al. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. 2010 Feb;106(2):86–94. doi: 10.1111/j.1742-7843.2009.00494.x
32. World Health Organisation. International classification of diseases for oncology. 3rd ed. Geneva: World Health Organisation; 2019.
33. Steliarova-Foucher E, Stiller C, Lacour B, et al. International classification of childhood cancer, third edition. Cancer. 2005 Apr 1;103 (7):1457–1467. doi: 10.1002/cncr.20910
34. Pukkala E, Engholm G, Hojsgaard Schmidt LK, et al. Nordic cancer registries – an overview of their procedures and data comparability. Acta Oncologica. 2018 Apr;57(4):440–455. doi: 10.1080/0284186X.2017.1407039
35. Barlow L, Westergren K, Holmberg L, et al. The completeness of the Swedish cancer register – a sample survey for year 1998. Acta Oncologica. 2009;48(1):27–33. doi: 10.1080/02841860802247664
36. Larsen IK, Smastuen M, Johannesen TB, et al. Data quality at the cancer registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer. 2009 May;45(7):1218–1231. doi: 10.1016/j.ejca.2008.10.037
37. Jokela M, Leinonen MK, Malila N, et al. Completeness of pediatric cancer registration in the Finnish cancer registry. Acta Oncol. 2019 Nov;58(11):1577–1580. doi: 10.1080/0284186X.2019.1638522
38. Leinonen MK, Miettinen J, Heikkinen S, et al. Quality measures of the population-based Finnish cancer registry indicate sound data quality for solid malignant tumours. Eur J Cancer. 2017 May;77:31–39. doi: 10.1016/j.ejca.2017.02.017
39. Wood ME, Lapane KL, van Gelder M, et al. Making fair comparisons in pregnancy medication safety studies: an overview of advanced methods for confounding control. Pharmacoepidemiol Drug Saf. 2018 Feb;27(2):140–147. doi: 10.1002/pds.4336
40. Bate A, Lindquist M, Edwards IR, et al. A bayesian neural network method for adverse drug reaction signal generation. Pharmacoepidemiol Prescription. 1998;54(4):315–321. doi: 10.1007/s002280050466
41. Chan CL, Rudrappa S, Ang PS, et al. Detecting signals of disproportionate reporting from singapore's spontaneous adverse event reporting system: an application of the sequential probability ratio test. Drug Saf. 2017;40(8):703–713. doi: 10.1007/s40264-017-0531-4
42. Berry SM, Berry DA. Accounting for multiplicities in assessing drug safety: a three-level hierarchical mixture model. Biometrics. 2004;60 (2):418–426. doi: 10.1111/j.0006-341X.2004.00186.x
43. R core team. R: a language and environment for statistical computing. Vienna Austria (VA): R Foundation for Statistical Computing; 2022.
44. Sturmer T, Rothman KJ, Avorn J, et al. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution–a simulation study. Am J Epidemiol. 2010 Oct 1;172(7):843–854. doi: 10.1093/aje/kwq198
45. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011 May;46(3):399–424. doi: 10.1080/00273171.2011.568786
46. Sturmer T, Wyss R, Glynn RJ, et al. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med. 2014 Jun;275 (6):570–580. doi: 10.1111/joim.12197
47. Park G, Jung H, Heo S-J, et al. Comparison of data mining methods for the signal detection of adverse drug events with a hierarchical structure in postmarketing surveillance. Life. 2020;10(8):138. doi: 10.3390/life10080138
48. Chen M, Zhu L, Chiruolu P, et al. Evaluation of statistical methods for safety signal detection: a simulation study. Pharmaceut Statist. 2014;14(1):11–19. doi: 10.1002/pst.1652
49. Sturmer T, Webster-Clark M, Lund JL, et al. Propensity score weighting and trimming strategies for reducing variance and bias of treatment effect estimates: a simulation study. Am J Epidemiol. 2021 Aug 1;190(8):1659–1670. doi: 10.1093/aje/kwab041